Wey - clinical

22.4.91

1098

JULY 1990 VOL 74 NO 7

BRITISH JOURNAL OF OPHTHALMOLOGY

(29)

Editorials

385 Diabetes and retinal function *Redmond Smith*

386 Natural history of epiretinal membranes *Redmond Smith*

387 Diabetic retinopathy; a new clue in the puzzle *Redmond Smith*

Original articles

388 Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy *Toke Bek, Henrik Lund-Andersen*

393 Variation in epiretinal membrane components with clinical duration of the proliferative tissue *I Morino, P Hiscott, N McKechnie, I Grierson*

400 Hypoxic viscosity and diabetic retinopathy *T Rimmer, J Fleming, E M Kohner*

405 A single dose of the topical carbonic anhydrase inhibitor MK-927 decreases IOP in patients *N Pfeiffer, R Hennekes, E A Lippa, F Grehn, H Garus, F L Brunner-Ferber*

409 Effects of topical timolol (0·5%) and betaxolol (0·5%) on corneal sensitivity *S S Weissman, P A Asbell*

413 Comparison of the effect of acetazolamide tablets and Sustets on diurnal intraocular pressure in patients with chronic simple glaucoma *P W Joyce, K B Mills*

417 Outcome of iatrogenic choroidal neovascularisation in sickle cell disease *Peter D Fox, Robert W Acheson, Graham R Serjeant*

421 The eye in the CHARGE association *I M Russell-Eggitt, K D Blake, D S I Taylor, R K H Wyse*

427 Electrophoretic assessment of aqueous and serum neurone-specific enolase in retinoblastoma and ocular malignant melanoma *B S F Shine, J Hungerford, B Vaghela, G A K Sheraidah*

Mini review

431 Ocular fluorophotophotometry *D J Spalton*

Case reports

433 Endogenous *Nocardia asteroides* endophthalmitis in a patient with systemic lupus erythematosus *Y Ishibashi, R Watanabe, S Hommura, A Koyama, T Ishikawa, Y Mikami*

437 Primary orbital liposarcoma: clinical and computed tomographic features *Alan A McNab, Ivan Moseley*

440 Inflammation of the retinal pigment epithelium: a unique presentation of ocular schistosomiasis *A Jane Dickinson, A Ralph Rosenthal, Karl G Nicholson*

443 Acute retinal necrosis as a novel complication of chickenpox in adults *T Matsuo, M Koyama, N Matsuo*

445 Frontal bone epidermoid – a rare cause of proptosis *C R Chowdhury, C M Wood, P R Samuel, J Richardson*

447 **Letters to the editor** **Book reviews** **Notes**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

CUK-H05934-20-P25369

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE
Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor *British Medical Journal*

P25369

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced*.

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof, and should read it carefully for printers' errors. Alterations to the original text should be kept to a minimum and may be charged to the author.

REPRINTS may be ordered from the Publishing Manager when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Ophthalmology*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not, however, required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents of the publication without prior permission is always illegal.

NOTICE TO ADVERTISERS Applications for advertisement space and for rates should be addressed to the Advertisement Manager, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *British Journal of Ophthalmology* is published monthly. The annual subscription rates are £106.00 inland and £126.00 overseas (US $200.00). Orders should be sent to the Subscription Manager, British Journal of Ophthalmology, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. All inquiries regarding air mail rates and single copies already published should be addressed to the Publisher in London.

Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR and
printed by
Paramount Printing Co
Ltd, Hong Kong

“Humphrey makes quality perimetry affordable”

You may think that acquiring a Humphrey Field Analyser is going to cost you as much as your yag laser. Read on.

The Humphrey Field Analyser is a modular system — In fact it is the only one in the world which is!

You can start with a basic model 605 which will give you all your screening requirements and then add to it as your needs develop even to a top of the range instrument like the model 640 which has full threshold facilities, analysis and data storage all in one.

Your Options

Model	Features
605	Screening programs and eye telescope
606	Screening programs and video eye monitor
610	Screening and threshold programs, eye telescope
611	Screening and threshold programs, video eye monitor

Model	Features
620	Screening and threshold programs, eye telescope, dual disk drives
630	Screening and threshold programs, video eye monitor, dual disk drives
640	Screening, threshold programs, video eye monitor, hard disk

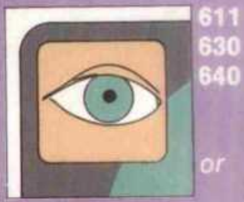
Humphrey Field Analysers are recognised as the industry standard by glaucoma management professionals worldwide. With over 4,000 sold Humphrey is the perimeter of choice both clinically and in research and teaching institutions.

And the cost: **From £6,995.00**

Ring **Claire Austin** *today on* **(0494) 427030** *for an up-to-date quotation or price list.*

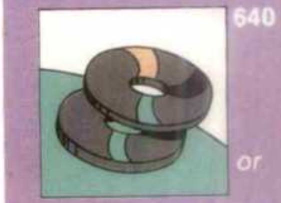
ALLERGAN HUMPHREY

The option of an eye telescope gives you control over alignment and fixation at minimal cost.

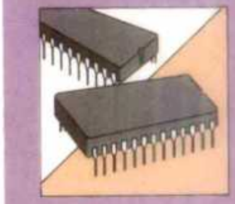


Choosing a video eye monitor instead makes this job much easier.

Floppy disks for storing and comparing fields can be added at any time.



The hard disk option will keep 33,000 patients' records inside your field analyser.



Software is easy to insert. If you only have a screening instrument you can add thresholding, and statistical analysis at any time.

VISUAL FIELDS

USED TO TREAT OVER 2 MILLION PATIENTS
USED IN 153 COUNTRIES
OVER 1,000 CLINICAL PAPERS PUBLISHED —

WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blocke should be withdrawn gradually.

Do not use in patients with soft contact len

Mydriasis resulting from use of 'Timoptol' with adre aline reported occasionally. Potentially, hypotensio and/or marked bradycardia may result from additio of 'Timoptol' to a calcium antagonist, rauwolfi alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children. *Nursing:* Mother should either stop nursing or stop 'Timoptol'. *Pregnancy:* Not studied weigh benefit against possible hazards.

SIDE EFFECTS

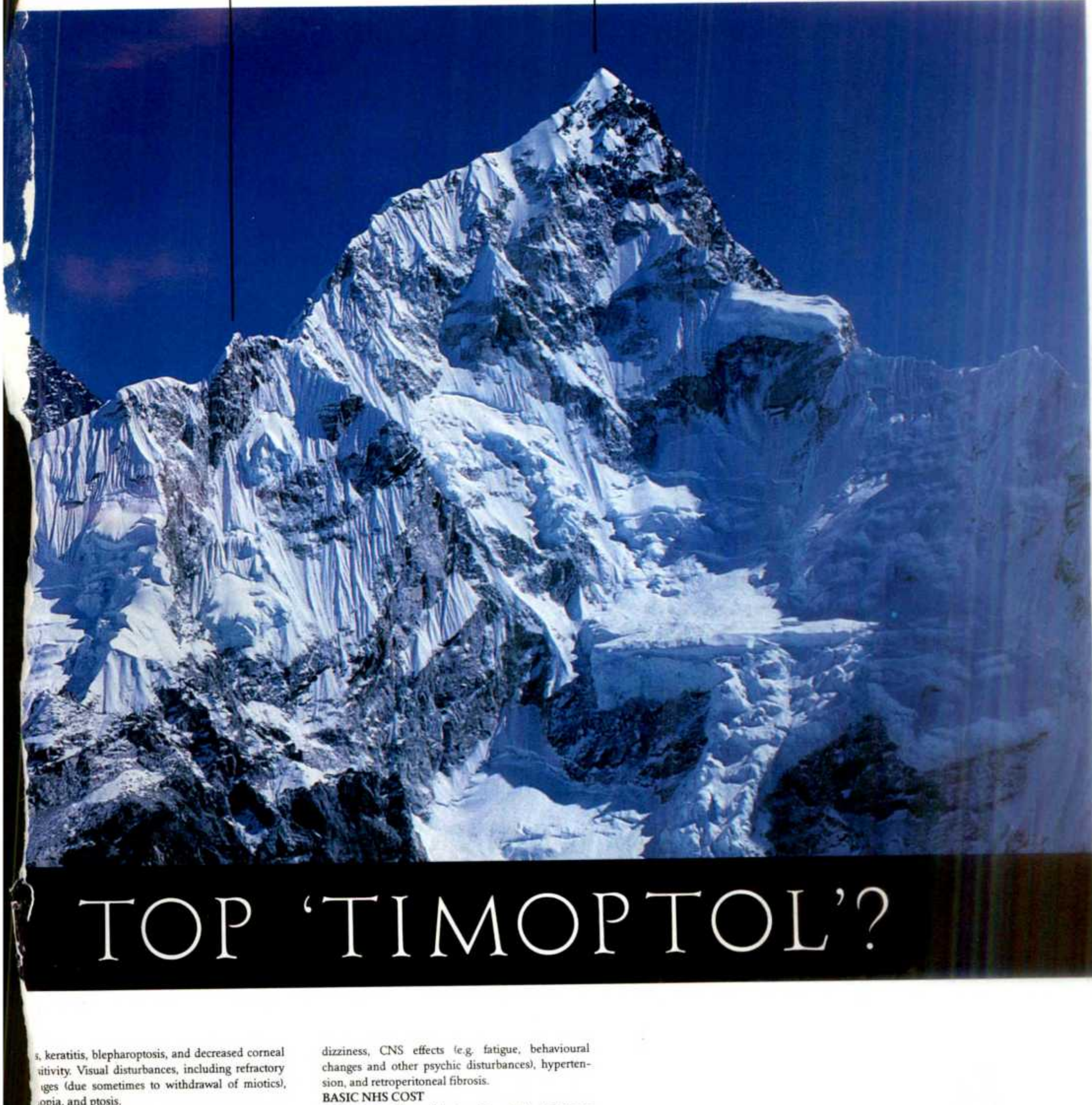
Ocular irritation, including conjunctivitis, blepha

12-90 TOT.89 GB 4697 J

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
PEN-ANGLE GLAUCOMA
ERAPY BY THE MAJORITY
UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE



TOP 'TIMOPTOL'?

s, keratitis, blepharoptosis, and decreased corneal
itivity. Visual disturbances, including refractory
ges (due sometimes to withdrawal of miotics),
opia, and ptosis.
dycardia, arrhythmia, hypotension, syncope,
art block, cerebrovascular accident, cerebral
haemia, congestive heart failure, palpitation,
rdiac arrest.
ronchospasm (predominantly with pre-existing
ronchospastic disease), respiratory failure, dyspnoea.
eadache, asthenia, nausea, dizziness, depression.
ypersensitivity, rash, and urticaria.
actions with an unestablished relationship are
MO, dry mouth, anorexia, dyspepsia, nausea,
dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST

0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack. 0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

Product licence numbers:

0.25% Ophthalmic Solution 'Timoptol', 0025/0134.
0.5% Ophthalmic Solution 'Timoptol', 0025/0135.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference

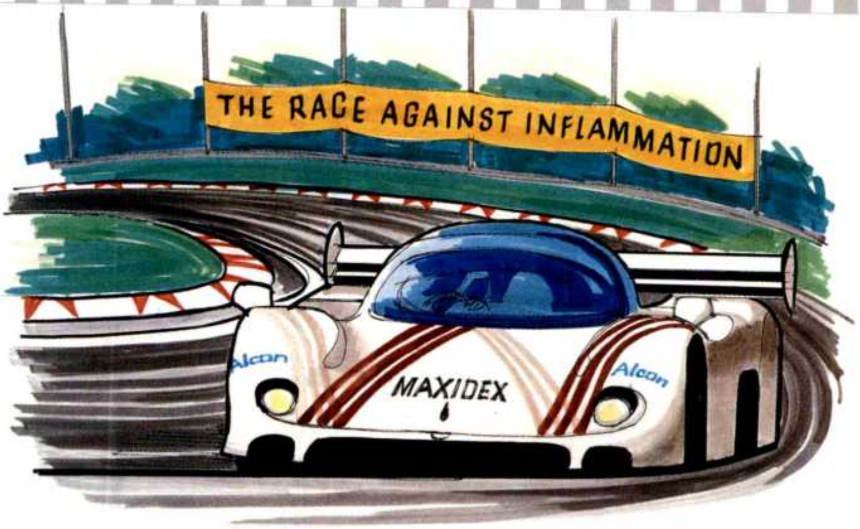
1. Data on file, Merck Sharp & Dohme Limited.

Ophthalmic Solution

Timoptol®

(timolol maleate, MSD)

NSURPASSED AS FIRST-LINE GLAUCOMA THERAPY



FAST THROUGH CORNEAS.

Maxidex ophthalmic suspension has proven to be a fast and effective treatment for intraocular inflammation.

Fast, because human studies[1] show that levels of dexamethasone were detectable in aqueous humour 20 minutes after topical administration of Maxidex — demonstrating rapid penetration of the human cornea.

MAXIDEX®
Dexamethasone
Ph. Eur. 0.1%
FAST & EFFECTIVE

Effective, because in the same studies peak levels of dexamethasone were achieved in human aqueous between 91 and 120 minutes after instillation of Maxidex.

Furthermore, 75% of peak concentration is still present after 4 hours, thus maintaining adequate levels between doses.

For full information contact Alcon Laboratories.

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford, Herts. WD2 4YR
Tel (0923) 246133 Fax (0923) 243331

REFERENCE:1. Watson, D. et al.: Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humor, Arch Ophthalmol 106: 686 687, 1988.

PRODUCT INFORMATION: Presentation: Dexamethasone PhEur 0.1% in a sterile, isotonic, ophthalmic suspension preserved with Benzalkonium Chloride BP 0.01%. **Uses:** Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and administration:** One or two drops topically in the conjunctival sac(s) four to six times daily. In severe disease, drops may be used hourly. **Contra-indications:** Epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; tuberculosis of the eye; and in those persons who have shown hypersensitivity to any component of this preparation. **Warnings:** Use in the treatment of herpes simplex requires great caution. Not effective in the treatment of Sjorgen's keratoconjunctivitis. Infection appears to be enhanced with the presence of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. It is advisable that the intraocular pressure be checked frequently. This product contains benzalkonium chloride and should not be used when soft contact lenses are being worn. **Adverse reactions:** Glaucoma with optic nerve damage, visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe may occur. **Pregnancy warning:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long-term treatment of pregnant patients. **Legal category:** POM. **Package quantities:** 5 ml and 10 ml. **P.L.:** 0649/5914.

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Diabetes and retinal function

The article in this issue entitled 'Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy' provides food for thought. The authors, Bek and Lund-Andersen, studied the retinal sensitivity to light of small areas of retina where diabetic damage had been positively identified by fluorescein angiography. To their surprise they were unable to demonstrate failure of retinal function even where severe damage, giving rise to gross breakdown of the blood-retinal barrier, could be shown. Aggregations of exudates produced scotomata but only where there was enough to mask the underlying retina.

The authors' main conclusion, on the basis of the techniques used, is that breakdown of the blood-retinal barrier is an earlier event than disturbance of neurosensory function. But it is the techniques used of which one has to take careful note before assuming that the diabetic process does not affect neural function via the vascular system but via some other subtle, as yet undiscovered biochemical mechanism. For the question has to be asked: in a sensory organ how can aberrations in performance due to true abnormalities of function be accurately assessed? From our experiences with correlating optic nerve and disc damage in glaucoma with visual fields it is obvious that deficit in sensory 'performance' tends to lag far behind clinical and even histopathological evidence of nerve damage. Linking optic nerve changes with visual field changes is not very different from attempting the same exercise with the retina itself. While accepting the authors' conclusions subject to the proviso they wisely insist upon, one suspects that the real problem may lie not so much in a mysterious absence of abnormality where abnormality would be expected but rather in an inability to demonstrate abnormality by the means at our disposal. One has to accept the fact that the eye's sensory performance is so fantastically sensitive that it can appear to be relatively unscathed even in the face of substantial damage. I well remember a dramatic demonstration of retinal sensitivity by Rushton at a lecture he gave some years ago in University College. He dropped a piece of blackboard chalk on the desk and announced that the energy liberated by the impact would have been enough to stimulate (adequately) all the cones of all the men who had ever lived and all the women too.

A glance through the literature on diabetic retinopathy reveals that, for the last few years at least, virtually every paper has been concerned with the vascular aspects or at least their immediate sequelae. In attempting to glean some sort of evidence from the literature as to the likelihood of there being mechanisms involved in diabetic retinal malfunction independent of vascular changes one is impressed by the small number of papers to be found. Most of the papers in this category have tended to be on rather high-powered experimental pathology. There have, for example, been several studies on experimental diabetes produced by injection of streptozotocin into rats. In one of these a reduction in thickness in the outer nuclear layer of the retina was induced by exposure to light,[1] and in another[2] the effects of aldose reductase inhibition of the retina was studied. Improvement in electrodiagnostic test results was found, but it was thought that this might have been associated with changes in the thickness of the capillary basement membrane. However, MacGregor *et al*[3] found evidence in experimentally diabetic rabbits that diabetes affects the metabolism of retinal structures independently of vascular disease. There are papers on colour vision in diabetes,[4,5] contrast sensitivity,[6] macular recovery time (nyctometry), and visually evoked responses (VER),[7] though in the last paper the degree of effect on the VER seemed to depend on the amount of vascular damage. But apart from these virtually every other paper is about anomalies in the vascular system, ranging from the most minute and esoteric details of the biochemistry of the capillary wall to the heroic surgery needed in advanced cases of proliferative retinopathy.

In summary, therefore, the more you look through the literature, the more unconvinced you are of anything other than vascular abnormalities causing visual damage in diabetic retinopathy. One intriguing point appeared in a paper by Bresnick and coworkers.[8] It appears that the 'capillary free zone' round the fovea is larger in diabetics than in controls. A corollary to this is that areas of capillary closure do not give rise to fluorescein leakage. Can one therefore postulate that there might be areas of relative underperfusion in diabetics which could give rise to visual deficit without showing fluorescein leakage? The snag with this theory, however, is that not only did Bek and Lund-Andersen not find areas of visual deficit in zones of leakage, but they did not find them in other zones either.

REDMOND SMITH

1 Johnson DD, O'Steen WK, Duncan TE. Photically-induced retinal damage in diabetic rats *Curr Eye Res* 1986, 5: 1–7
2 Kosak WM, Marker NA, Elmer KK Effects of aldose reductase inhibition of the retina and health indices of streptotozocin-diabetic rats *Doc Ophthalmol* 1986, 64· 355–77.
3 MacGregor LC, Rosecan LR, Laties AM, Matschinsky FM. Altered retinal metabolism in diabetes 1. Microanalysis of lipid, glucose, sorbitol, and myo-inositol in the choroid and in the individual layers of the rabbit retina *J Biol Chem* 1986, 261: 4046–61
4 Bresnick GH, Condit RS, Palta M, Korth K, Groo A, Syrjala S Association of hue discrimination loss and diabetic retinopathy *Arch Ophthalmol* 1985; 103· 1317–24.
5 Suszuki R Visual function in diabetic retinopathy *Philipp J Ophthalmol* 1984, 16: 79–81
6 Della Sala S, Bertoni G, Somazzi L, Stubbe F, Wilkins AJ Impaired contrast sensitivity in diabetic patients with and without retinopathy, a new technique for rapid assessment. *Br J Ophthalmol* 1985; 69: 136–42
7 Collier A, Mitchell JD, Clarke BF Visual evoked potential and contrast sensitivity function in diabetic retinopathy *Br Med J* 1985; 291: 248
8 Bresnick GH, Condit R, Syrjala S, Palta M, Groo A, Korth K. Abnormalities of the foveal avascular zone in diabetic retinopathy *Arch Ophthalmol* 1984, 102: 1286–93

British Journal of Ophthalmology, 1990, 74, 386

Editorial

Natural history of epiretinal membranes

The first thing one needs to know about in considering the article by Morino and colleagues in this month's issue is the classification of collagen. The paper mentions four types, and the authors considerately give us some clues about them (see 'Material and methods'). Type I is in scars; type II is in the vitreous; type III is also found in scars, and the distinction from I is not entirely clear to me except that, paradoxically, it occurs late in scars, whereas III occurs early; and finally type IV is a component of basement membranes. As well as the collagens there are other proteins in the membranes. They give clues to glial (glial fibrillary acidic protein, GFAP), epithelial (cytokeratin), and basement membrane (laminin) elements; there is also fibronectin, which is important during healing processes. The object of the study was to analyse membranes for their proportionate content of these various elements and then see if this could be related to the 'age' of the membrane and/or the clinical type.

It will be appreciated that there are at least two distinct classes of epiretinal membranes, those associated with ordinary hole-bearing retinal detachments and those rather mysterious ones causing macular pucker. Rather as one would expect, the latter type do not contain pigment epithelial cells whereas the others do. The present article is about the membranes associated with detachment, in other words the membrane of proliferative vitreoretinopathy (PVR).

Membranes were classified as early or late according to the known duration of the PVR (less or more than three months). The cellular content did not differ greatly between early and late membranes, but there was a tendency for retinal pigment epithelial (RPE) cells to disappear from some of the late membranes, whereas glial cells tended to persist.

So far as extracellular material was concerned, all contained collagen types I, III, and IV, and type II was present in only 70% of membranes and was a minor component where it did appear. Collagen types I and III were the most abundant. This indeed is not altogether surprising if, as stated at the outset, these collagens are associated with scarring. Fibronectin was present in all membranes but most prominent in the early ones; again this is a protein associated with healing mechanisms. A peculiar thing about the association of collagen types I, III, and IV with glial cells was that only some glial cells seemed to be associated. In other words the distribution of the collagen was patchy, and indeed the distribution of the other proteins – fibronectin and laminin – was erratic as well. The paper gives full details, but the association of the various proteins with the various other types of cells found in the membranes (fibroblasts, cytokeratin negative or positive, or plump RPE cells), was again erratic and difficult to summarise, with the exception that the fibroblasts in all the epiretinal membranes were associated with fibronectin.

The main conclusion is that glial cells seem to figure prominently in the natural history of these membranes. They persist and even relatively increase with time and are unlikely to be artefactual. RPE elements, however, seem to decline with the passage of time, even those RPE cells which had lost their original plump form and had undergone metaplasia to a fibroblast-like appearance.

This is a rather difficult article for clinicians to read and to fully understand, but nevertheless the conclusions in the last few paragraphs are particularly interesting, as the authors try to pull together the complex findings to arrive at a reasonable understanding of the laminar nature of these peculiar membranes and their 'peelability'. In the final paragraphs the authors give a closely argued and convincing account of their conclusion that, in contrast to what has from time to time been suggested, glial cells probably play an important part in the production of PVR membranes but are not the sole elements. Furthermore the ingenious suggestion is made that other cellular elements participating in the process tend to generate a tendency to lamination in these membranes which may favour 'peelability' layer by layer.

As an ophthalmologist who has never tried peeling a membrane, the whole exercise has always struck me as likely to be so difficult as to be well-nigh impossible. The fact that it is sometimes so successful is certainly a tribute to the persistence of the originators of this form of surgery, just as the present article demonstrates the ingenuity and persistence of the basic scientists working in the same field.

REDMOND SMITH

British Journal of Ophthalmology, 1990, 74, 387

Editorial

Diabetic retinopathy; a new clue in the puzzle

The last sentence but one in the article by Rimmer, Fleming, and Kohner in this month's issue reads, 'The phenomenon of hypoxic viscosity could be important because it might present a new target for pharmacological attack.' This had a familiar ring, and I managed after some thought to recall why. I had used a somewhat similar phrase myself when writing about the possible anoxic basis for rubeosis in neovascular glaucoma: 'When pathology is understood, rational treatment may follow'.[1] Unfortunately the word 'may' is especially important in the foregoing sentence. One of the most frustrating things in medicine is to understand the pathology and not be able to do anything about it so far as an individual patient is concerned. Many of the inherited diseases come into this category. Killing off affected fetuses may be one way of pre-empting the problem, but it doesn't help a living patient. I see that I am wandering from my subject.

Does the paper from Rimmer and colleagues get us any further in our quest for control of diabetic retinopathy? As the paper reminds us, retinopathy is now the commonest cause of blindness in people of working age in the UK and USA. Present treatment is directed rather at the results of the retinopathy (neovascularisation and haemorrhage),[2] as indeed is the treatment for rubeosis and sickle cell retinopathy.

It is of interest that it took the retinal hypoxic theory of neovascularisation, first proposed by Michaelson[3] in 1948, more than 10 years to yield any fruit in the form of treatment. The first retinal ablations performed for the specific purpose of treating remote neovascularisation were not reported until 1961.[4] One certainly hopes that, if other workers confirm the claim of Rimmer and colleagues to have established a working hypothesis to tie together their previous observation[5] of slowing of the retinal blood flow in patients with retinopathy (by entoptic blue light studies), this will lead rapidly to advances in treatment of this damaging condition.

For a clinician such as myself to speculate on what might be possible in the realm of what I believe goes under the mysterious title of rheology would be unwise. Indeed the very writing of this editorial makes me feel vulnerable to the scorn of experts on the subject, and I would not have written it if the expert we had lined up to do it had not been unavoidably prevented from producing it at the last moment. Nevertheless even the ordinary clinician can see at once what a fantastic advance it might be were there to be developed a means of preventing the retinopathy rather than just trying to stave off its worst consequences, as at present. When one considers the numerous examples of the deleterious consequences of retarded blood flow which can be found in the various tissues of the body, from the simple example of varicose veins upwards, one fears that an answer to the problems possibly caused by retarded venous flow in the eye may be slow in coming. One may be left in the frustrating situation mentioned at the beginning of this editorial where the pathology is better understood but rational treatment has yet to be devised. This certainly would not detract from the merits of what might prove to be a genuine advance in the understanding of diabetic retinopathy on the part of the Hammersmith group.

REDMOND SMITH

1 Smith RJH. Neovascular glaucoma experience over 28 years *Proceedings of the 24th International Congress of Ophthalmology* 1982 1: 624–6
2 Meyer-Schwickerath G Treatment of Eales' disease and diabetic retinopathy with photocoagulation *Trans Ophthalmol Soc UK* 1964, 84: 67–76
3 Michaelson IC The mode of development of the vascular system of the retina, with some observations on its significance for certain retinal diseases *Trans Ophthalmol Soc UK* 1948; 68: 137–80
4 Smith RJH Neovascularisation in ocular disease *Trans Ophthalmol Soc UK* 1961, 81: 125–44
5 Rimmer T, Fallon TJ, Kohner EM Long term follow-up of retinal blood flow in diabetes using the blue light entoptic phenomenon *Br J Ophthalmol* 1989, 73· 1–5

British Journal of Ophthalmology, 1990, **74**, 388–392

ORIGINAL ARTICLES

Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy

Toke Bek, Henrik Lund-Andersen

Abstract

Twenty patients with insulin dependent diabetes mellitus were selected on the basis of morphological signs of blood-retinal barrier leakage – namely, hard exudates seen on fundus photographs and/or localised leakage of fluorescein seen on fluorescein angiograms. Computerised perimetry was carried out in visual field areas that corresponded to the morphological lesions, and the visual field data were accurately correlated with the morphology as seen on fundus photographs and fluorescein angiograms. In addition, in seven of the patients who represented the range of leakage among the patients studied, the blood-retinal barrier leakage was quantitated by vitreous fluorophotometry. In 16 cases normal light sensitivity was found in retinal areas showing localised leakage as studied on fluorescein angiograms. In four cases with pronounced maculopathy, where scotomata occurred, there was no topographical correlation between the scotomata and barrier leakage. Furthermore hard exudates often, but not consistently, caused localised scotomata when arranged in dense conglomerates. The permeability values correlated with angiographically observed hyperfluorescence in the macular area. On the basis of the techniques employed in the present study it seems that breakdown of the blood-retinal barrier is an earlier event than disturbance of neurosensory function in the development of diabetic retinopathy. However, the findings give no evidence of a causal relationship between barrier leakage and damage to sensory cell function.

Department of Ophthalmology, University of Copenhagen, Gentofte Hospital, 2900 Hellerup, Denmark
T Bek
H Lund-Andersen

Correspondence to: Toke Bek, MD, Department of Ophthalmology, University of Copenhagen, Gentofte Hospital, 2900 Hellerup, Denmark.

Accepted for publication
2 February 1990

Diabetic retinopathy displays a complex morphological picture which results from retinal ischaemia, new vessel formation, and breakdown of the blood-retinal barrier.[1] Some studies have suggested that breakdown of the blood-retinal barrier leakage is an early, or perhaps the earliest, sign of pathology in the development of retinopathy.[1,2] This barrier leakage can be studied qualitatively on fluorescein angiograms[3] by detecting localised hyperfluorescence that increases and diffuses through the angiographic phases, and signs of barrier leakage can be seen on fundus photographs as hard exudates, which are assumed to be precipitates of lipoprotein exuded from the blood stream. Furthermore, a quantitative estimate of blood-retinal barrier leakage can be obtained by vitreous fluorophotometry.

Some authors have alternatively proposed that the earliest sign of pathology in diabetic retinopathy might be a disturbance of neurosensory function.[4-6] Although pronounced fluorescein leakage in the macular area as studied on fluorescein angiograms is often associated with decreased visual acuity, the association between barrier leakage and neurosensory function has not been examined in detail.

The purpose of the present study was to correlate signs of blood-retinal barrier leakage as seen on fundus photographs and fluorescein angiograms with neurosensory function as determined by computerised perimetry. To support the interpretation of the angiograms, vitreous fluorophotometry was done in seven patients who represented the range of leakage among the patients studied.

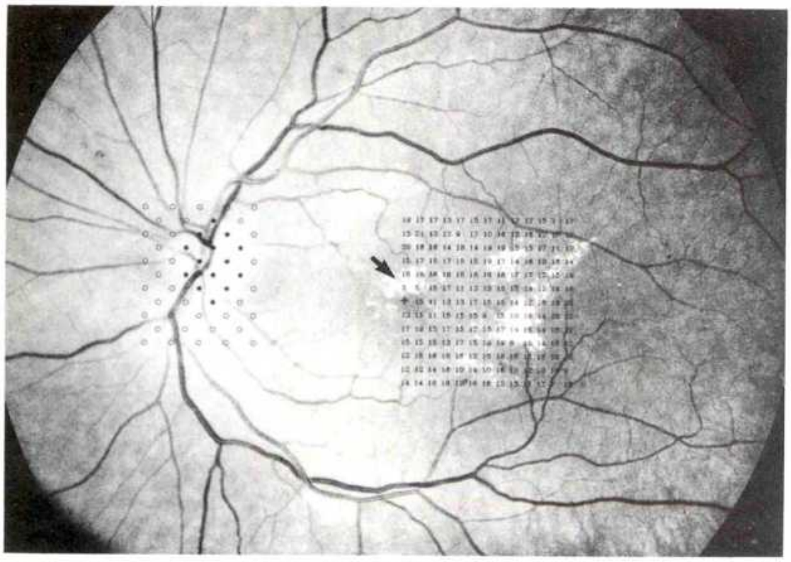


Figure 1A: Fundus photograph of a patient with formations of hard exudates in the macular area. The stimulus pattern extended from degree co-ordinates: (x,y)=(0,−6) to (x,y)=(12,6). The little conglomerate of hard exudates located over the point of fixation (arrow) is seen to cause a relative scotoma in the visual field.

Materials and methods

SUBJECTS

Twenty patients with insulin dependent diabetes mellitus and with signs of blood-retinal barrier leakage – namely, hard exudates seen on fundus photographs and/or localised leakage of fluorescein seen on fluorescein angiograms – were included. They had a routine ophthalmological examination including visual acuity, slit-lamp examination, tonometry, ophthalmoscopy, fluorescein angiography, and computerised perimetry. In addition vitreous fluorophotometry was carried out in seven of the patients. Informed consent was obtained.

The ametropia of the eyes ranged between −1·75 D and +4·5 D, and the most severe astigmatism was 1·25 DC. In four patients with pronounced maculopathy the best corrected visual acuity was 6/12–6/18. In all the other patients the visual acuity was 6/6. Except for funduscopic signs of retinopathy the other findings on ophthalmic examination were normal in all the patients.

PHOTOGRAPHY

Photography was performed with a Canon CF-60Z fundus camera employing Ektachrome 64 (EPR 135–36) film for fundus photography, and Ilford HP5 black-and-white film for fluorescein angiography. 5 ml 10% fluorescein sodium was injected into an antecubital vein for fluorescein angiography and vitreous fluorophotometry. Angiograms were taken of the central fundus in fast sequence during the filling phase of the vessels, and with regular intervals until 15 min after injection. Prior to photography cycloplegia and mydriasis were induced with metaoxedrine 10% and tropicamide 1% eyedrops.

PERIMETRY

Perimetry was carried out with a Humphrey Field Analyzer (HFA). Full-threshold examinations were performed in a stimulus pattern measuring 12°×12° with a density of 1°, Goldmann stimulus size I being employed. Since the minimum density of customised (individually defined) stimulus patterns on the HFA is 2°, four intersecting patterns with a displacement of 1° in the vertical and the horizontal plane were subsequently tested, and finally merged. The stimulus patterns were placed in areas of the visual field that approximately corresponded to the retinal areas where morphological lesions had been observed by prior funduscopic examination. Threshold values that deviated more than 5 dB from the expected value calculated on basis of answers from adjoining points were retested (standard procedure on the HFA). The blind spot was delimited with Goldmann stimulus size II with a single intensity of 10 dB in two special point patterns located in the area of the blind spot, one (pattern A) extending from degree co-ordinates (x,y)=(11,−7) to (19,3) and one (pattern B) from degree co-ordinates (x,y)=(12,−8) to (18,2). By merging these two patterns, a spatial resolution of 1·4° could be obtained in this area. All patients could see the perimeter screen sharply during perimetry without the addition of a corrective lens.

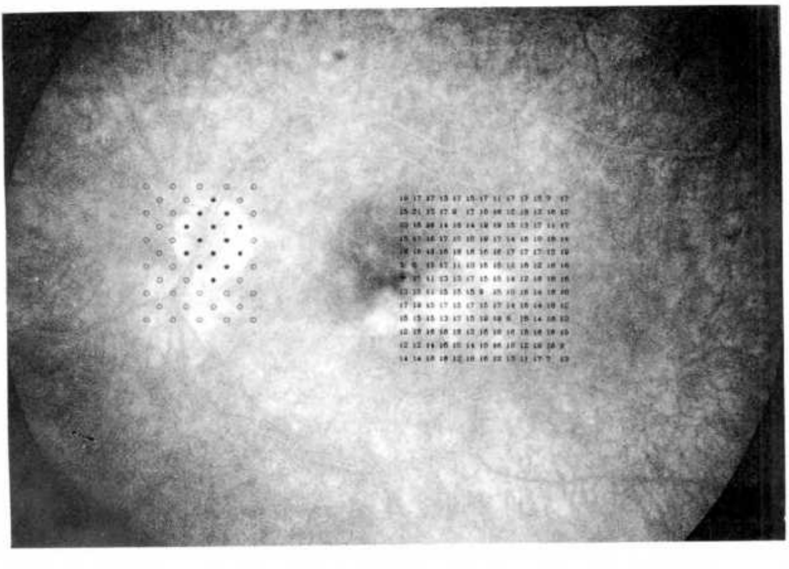


Figure 1B: Fluorescein angiogram from the same patient 592 s after intravenous injection of fluorescein. It can be seen that the decibel values located over the area displaying leakage do not differ from values located over normally appearing retina. Visual acuity was 6/6. Permeability: 2·2× 10^{-7} cm/s.

For control of baseline decibel values with Goldmann stimulus size I, 10 normal persons (volunteers), aged 25–56, with no prior history of ophthalmological disease were tested in one eye with full-threshold strategy employing programme 30-2 on the HFA. Decibel values in each stimulus point were averaged.

Fixation was continually checked on the fixation monitor supplied on the HFA, which displays the eye on a video screen during perimetry. Fixation was stable during all test sessions in all the patients and normal persons included.

SUPERIMPOSITION TECHNIQUE

The superimposition of visual field data on to fundus pictures was carried out according to a technique recently developed in our laboratory.[7] This technique is applicable to a fundus photograph (subtending approximately 60° with the camera employed here) with the foveal region in centre, and the accuracy of the overlay of visual field data on to the corresponding fundus photograph is better than 1°.

The technique was developed by establishing imaging in the fundus camera in an optical model. This model consisted of a concave spherical surface containing targets with known angular position and a lens in front of the sphere. By photographing the sphere through a +3 D lens located 0·33 m in front of (in the centre of) the sphere, imaging through the fundus camera when photographing the fundus of an emmetropic eye was simulated. By studying the location on the film of targets with known angular position in the sphere, camera distortion could be established. By subsequently varying the power of the lens and focusing the sphere through the lens, imaging in the fundus camera when photographing eyes with different degrees of ametropia was simulated. On photographs of the sphere the size of the photographic field of view as a function of ametropia could thereby be established.

With this knowledge of the optical imaging in the fundus camera, the visual field printout could be reduced in each patient to match the size of the corresponding fundus photograph. The visual field was inverted about a horizontal axis, and the overlay was subsequently done on a basis of two points of reference. One, the fixation

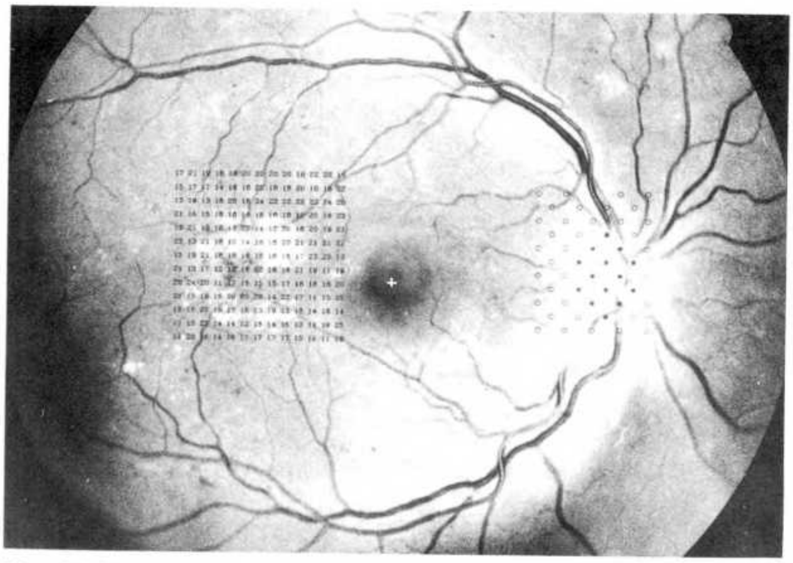


Figure 2A: Fundus photograph of a patient with circinate conglomerates of hard exudates temporal to the foveola. The stimulus pattern extended from degree co-ordinates $(x,y)=(-16,-4)$ *to* $(x,y)=(-4,8)$. *The exudates are seen not to cause any registrable decrease in retinal light sensitivity.*

point in the visual field, was laid over the foveola on the fundus picture; and the other, the blind spot in the visual field, was laid over the optic nerve head on the fundus picture.

VITREOUS FLUOROPHOTOMETRY

Vitreous fluorophotometry was carried out with the Fluorotron Master (Coherent, Palo Alto, California). Permeability values were calculated by relating the plasma time-integral of non-protein bound fluorescein at the time of measurement (approximately 60 min) to the fluorescein concentration profile in the vitreous body. The method is described in detail elsewhere.[8]

Results

In Figures 1 to 3 representative examples of visual field data correlated with corresponding fundus morphology are shown. In the point patterns used to delimit the blind spot closed circles indicate stimulus points not seen, whereas open circles indicate seen points. The fixation point is indicated with a cross. The numbers indicate decibel values obtained with Goldmann stimulus size I in the individually placed stimulus patterns, and each decibel value in the pattern has been placed over the corresponding retinal area. For points tested twice (see 'Materials and methods' section) the average of the two decibel values was employed.

In the normal volunteers the average of decibel values from each stimulus point showed a decrease of 0·4 dB/degree from the centre towards the periphery of the visual field, with an extrapolated value of 21 dB in the centre and ranging ±3 dB from this mean line. For all patients the decibel values in non-scotomatous areas were within the range of normal persons.

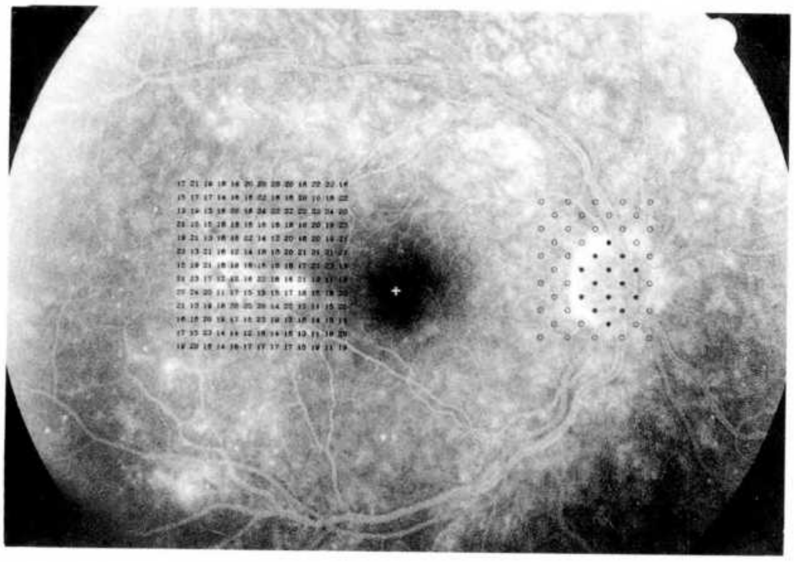


Figure 2B: Fluorescein angiogram of the same patient 405 s after intravenous injection of fluorescein. Localised retinal areas with pronounced leakage are seen to have normal light sensitivity. Visual acuity was 6/6. Permeability: $3{\cdot}8\times10-7$ *cm/s.*

No correlation was found between blood-retinal barrier leakage and retinal light sensitivity. In 16 patients who represented all degrees of barrier leakage there was normal light sensitivity in areas which displayed localised leakage (see Figs 1 and 2). In four patients localised scotomata occurred. These patients had pronounced morphological signs of maculopathy, in three cases including macular oedema (see Fig 3), and when the scotomata included the foveola there was an accompanying decrease in visual acuity. However, these scotomata did not correlate topographically with barrier leakage as studied on fluorescein angiograms; this is, localised leaking areas as well as localised non-leaking areas occurred in the same pattern over both normally and abnormally functioning retina.

The permeability values obtained by vitreous fluorophotometry ranged between $1{\cdot}2\times10^{-7}$ cm/s and $7{\cdot}0\times10^{-7}$ cm/s (mean normal value $1{\cdot}1\times10^{-7}$ cm/s (SD $0{\cdot}4)\times10^{-7}$ cm/s).[8] There was a correlation between the permeability value and macular hyperfluorescence as assessed on pictures of the late fluorescein angiographic phases. Furthermore, hard exudates often, but not consistently, caused scotomata in the visual field when arranged in dense conglomerates.

Discussion

In the present study computerised perimetry was carried out in 20 insulin dependent diabetic patients with funduscopic signs of break-down of the blood-retinal barrier, and the visual field data were accurately correlated with the corresponding morphology seen on fundus photographs and fluorescein angiograms. No correlation was found between retinal light sensitivity as determined by computerised perimetry and localised blood-retinal barrier leakage as studied by fluorescein angiography. However, hard exudates, which are assumed to be precipitates of lipoprotein exuded from the blood stream, often caused localised scotomata when arranged in larger conglomerates.

In the literature much attention has been directed towards establishing the nature of the initial pathophysiological event in the development of diabetic retinopathy. Several different views have been proposed. One view suggests that the initial event is a breakdown of the blood-retinal barrier,[1 2] and another view that it is a disturbance of neurosensory function caused by metabolic dysregulation.[4-6]

In the present study this question has been investigated by employing retinal light sensitivity as a measure of neurosensory function and leakage of fluorescein as a measure of blood-

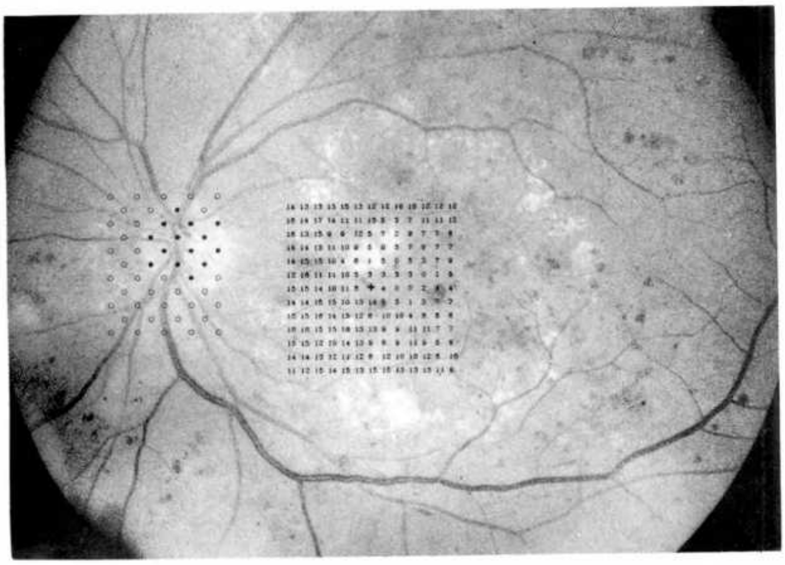
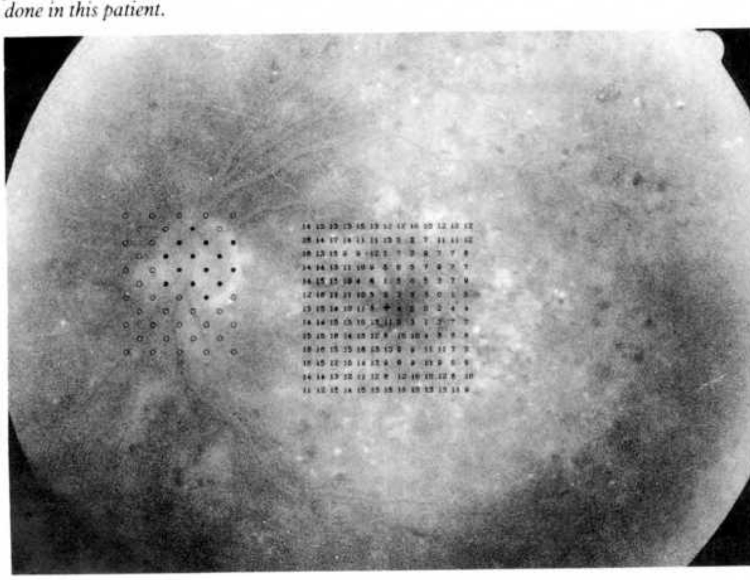


Figure 3A: Fundus photograph of a patient with pronounced diabetic maculopathy. The stimulus pattern extended from degree co-ordinates (x,y)= (−6,−6) to (x,y)=(6,6). Retinal oedema was detected in the whole macular area by stereo microscopic fundus examination.

retinal barrier breakdown. Blood-retinal barrier leakage was defined as localised hyperfluorescence that increased and diffused through the angiographic phases. The validity of this criterion was supported by the fact that in seven patients the permeability values obtained by vitreous fluorophotometry (referring only to leakage in the macular area[9]) correlated with the angiographically observed macular hyperfluorescence. In 16 patients who represented all degrees of barrier leakage there was normal light sensitivity in the areas displaying localised leakage, and in four patients with pronounced maculopathy where localised scotomata occurred no correspondence was found between the scotomata and barrier leakage as studied on fluorescein angiograms. Thus, if the techniques used are suitable for elucidating this question, it seems that the breakdown of the blood-retinal barrier is an earlier event than disturbance of neurosensory function in the development of diabetic retinopathy. However, since no topographical correlation was found between barrier leakage and decreased light sensitivity in any of the patients studied, the findings give no evidence of a causal relationship between barrier leakage and damage to sensory cell function. For a more certain statement about lack of causality to be made, however, a prospective study is needed in which barrier status is followed in retinal areas that later give rise to scotomata.

Figure 3B: Fluorescein angiogram of the same patient 569 s after intravenous injection of fluorescein. Pronounced spotwise and diffuse leakage is seen in the macular area. Visual acuity was 6/18, and a central scotoma is seen to include the point of fixation. The retinal areas displaying abnormal function (low decibel values) cannot be distinguished from normally functioning retina on the basis of barrier leakage. The decibel values in the left part of the stimulus pattern are normal. Vitreous fluorophotometry was not done in this patient.



It is likely that tissue damage caused by retinal oedema may have contributed to impairment of sensory cell function in some of the cases where scotomata occurred. However, the relation of retinal oedema to blood-retinal barrier leakage is rather difficult to evaluate, since oedema reflects the sum of net transcapillary fluid flow and production of metabolic water in the retinal tissue, whereas barrier leakage studied with fluorescein angiography and vitreous fluorophotometry almost exclusively refers to leakage out of the blood vessels.

The blood-retinal barrier system is composed of two barriers – an inner barrier consisting of the endothelial lining of the retinal capillaries, and an outer barrier consisting of the pigment epithelium. A differentiation of these two barriers is not possible by merely studying leakage on fluorescein angiograms. Leakage through each of these two barriers may indicate very different pathophysiological mechanisms – for the inner barrier a disturbance of the retinal vascular system, and for the outer barrier a disturbance of the pigment epithelium, which is supplied by the choroidal cirulatory system. Possible neuronal damage caused by breakdown of the two barriers might in theory be differentiated by determination of localised neurosensory function, for example, by employing computerised perimetry. Leakage through the outer barrier would be a consequence of disturbed function of the pigment epithelium and therefore possibly be accompanied by an impaired function of the sensory cells, eventually resulting in scotomata in the visual field. In contrast, leakage through the inner barrier would not primarily cause damage to retinal neurons and therefore, at least in the initial stages, not cause scotomata in the visual field. Provided such reasoning is valid, the findings of the present study seem to indicate that blood-retinal barrier leakage is mainly caused by a breakdown of the inner barrier. However, a technique for the true separation of the two barriers is needed in order to clarify this question.

When studying retinal light sensitivity in areas displaying localised blood-retinal barrier leakage the scotomata to be found, if any, must be expected to be small. Therefore appropriate stimulus conditions for the detection of small scotomata are required. In a recent study it has been established that the smallest stimulus size possible should be employed when dense stimulus patterns are used for the detection of small scotomata.[10] Thus the optimal stimulus parameters available on the HFA were chosen by combining Goldmann stimulus size I (subtending approximately 0·1°) with a stimulus density of 1°. It is evident that even with these stimulus parameters smaller lesions may easily have escaped detection. This may explain why isolated hard exudates did not result in a registrable decrease in retinal light sensitivity. However, some larger conglomerates of hard exudates also failed to cause scotomata, which would be expected from their size. Most probably the morphological entity of a hard exudate as seen by funduscopic examination covers lesions with a wide range of thickness and biochemical composition, and therefore also a wide range of translucency.

In conclusion, the findings of the present study seem to indicate that breakdown of the blood-retinal barrier is an earlier event than disturbance of neurosensory function in the development of diabetic retinopathy. However, the findings provide no evidence of a causal relationship between barrier leakage and damage to sensory cell function.

This study was supported by Mimi and Victor Larsen's Foundation, the John and Birthe Meyer Foundation, and Carl Larsen's Foundation.

The skilful assistance of photographer Hans Henrik Petersen and technician Bente Mertz is gratefully acknowledged.

1 Ashton N Pathogenesis of diabetic retinopathy. In: Little HL, Jack RL, Patz A, Forsham PH, eds *Diabetic retinopathy*. New York· Thieme-Stratton, 1983. 85–106.

2 Cunha-Vaz J, Faria De Abreu JR, Campos AJ, Figo GM Early breakdown of the blood-retinal barrier in diabetes *Br J Ophthalmol* 1975; 59: 649–56

3 Bresnick GH, Segal P, Mattson D Fluorescein angiographic and clinicopathologic findings In Little HL, Jack RL, Patz A, Forsham PH, eds *Diabetic retinopathy* New York Thieme-Stratton, 1983. 37–71.

4 Bloom A, Heath JH, Kelsey PR, Hunter PR, Bridgden WD. The use of the Roth-Keeler central field scotometer in the study of diabetic retinopathy. *Ophthalmic Res* 1972; 3: 166–73

5 Bresnick GH. Diabetic retinopathy viewed as a neurosensory disorder *Arch Ophthalmol* 1986; 104: 989–90.

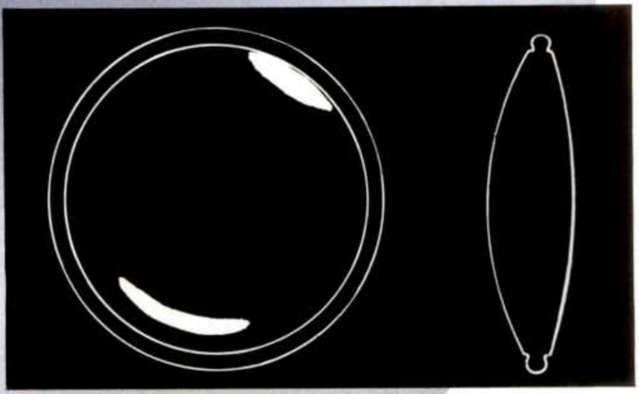
6 Simonsen SE ERG in diabetics. In. François J, ed. *The clinical value of electroretinography*. Fifth ISCERG Symposium, Ghent. Karger· Basel, 1966 403–12.

7 Bek T, Lund-Andersen H Accurate superimposition of visual field data onto fundus photographs. *Acta Ophthalmol (Kbh)* 1990; 68: 11–8.

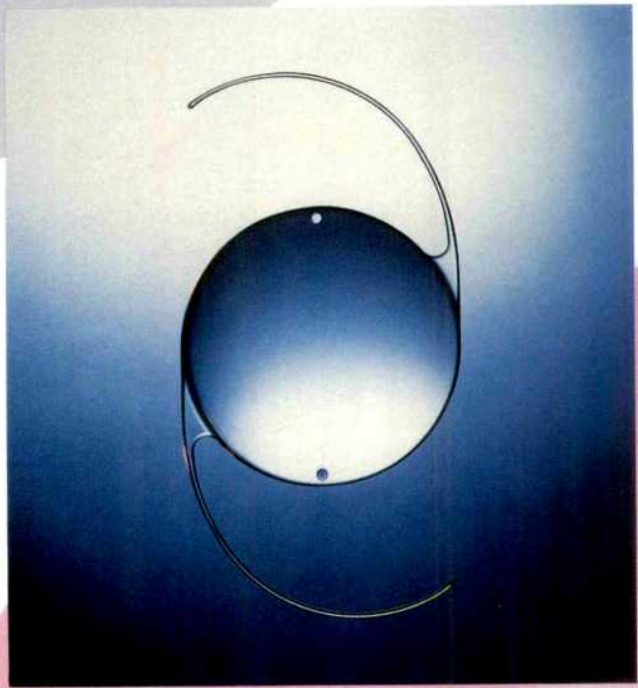
8 Lund-Andersen H, Krogsaa B, la Cour M, Larsen J Quantitative vitreous fluorophotometry applying a mathematical model of the eye. *Invest Ophthalmol Vis Sci* 1985; 5: 698–710.

9 Dalgaard P, Lund-Andersen H, Barker V Vitreous Fluorophotometry· mathematical analysis of the effect of peripheral leakage on axial scans *Invest Ophthalmol Vis Sci* 1989; 30: 1522–6.

10 Bek T, Lund-Andersen H The influence of stimulus size on perimetric detection of small scotomata. *Graefes Arch Clin Exp Ophthalmol* 1989; 227: 531–4



In 1949 there was only one Intraocular lens manufacturer in the World



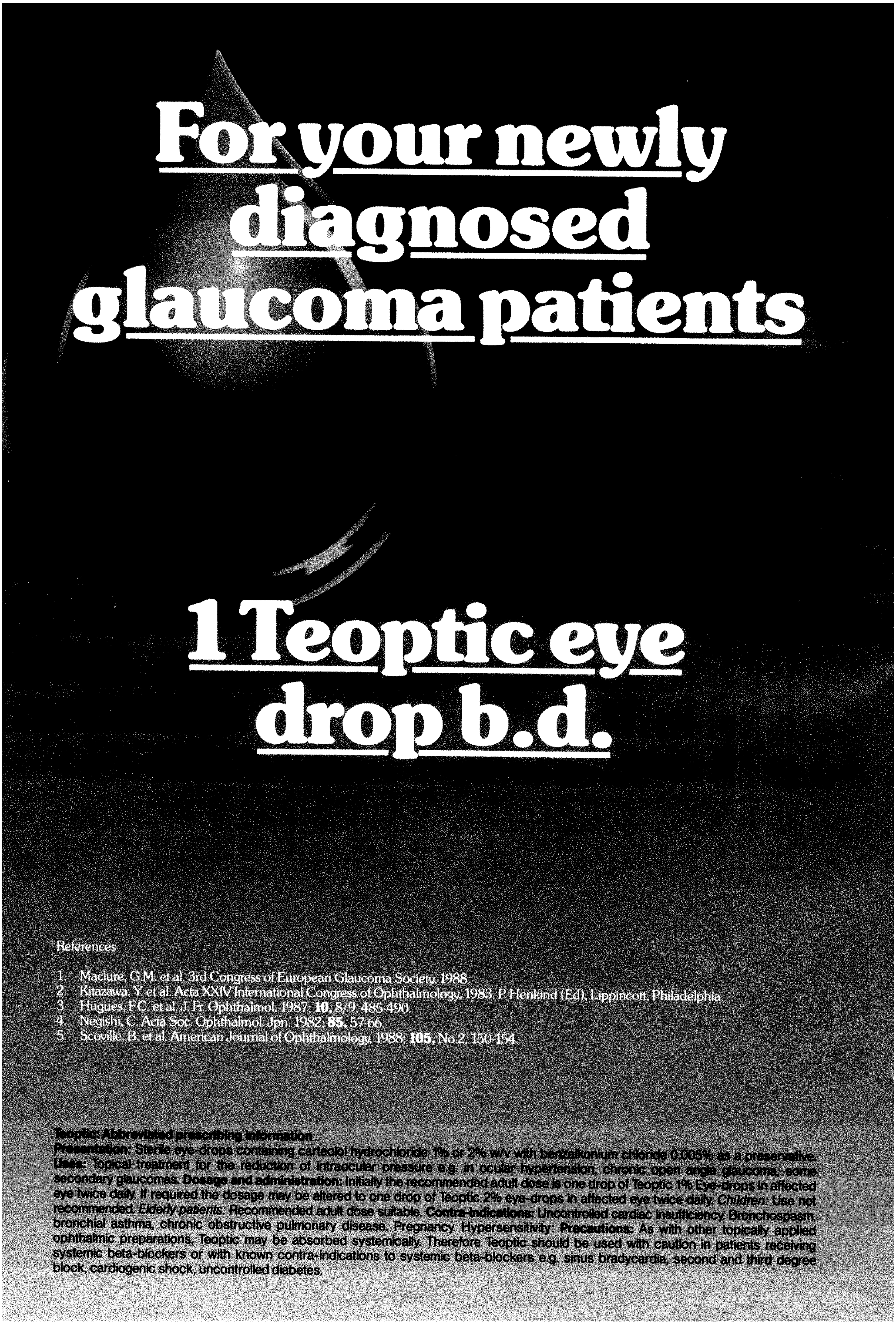
For many Ophthalmologists there still is,..

RAYNER

Rayner Intraocular Lenses Limited

Sackville Trading Estate, Sackville Road,
Hove, Sussex BN3 7AN, England
Telephone: (0273) 205401 (6 lines) Telex: 877744 (RILSTE G)
Fax: (0273) 24623

For over 40 years Rayner have been manufacturing
I.O.L's to meet the changing needs of
the World's Ophthalmologists.



For your newly diagnosed glaucoma patients

1 Teoptic eye drop b.d.

References

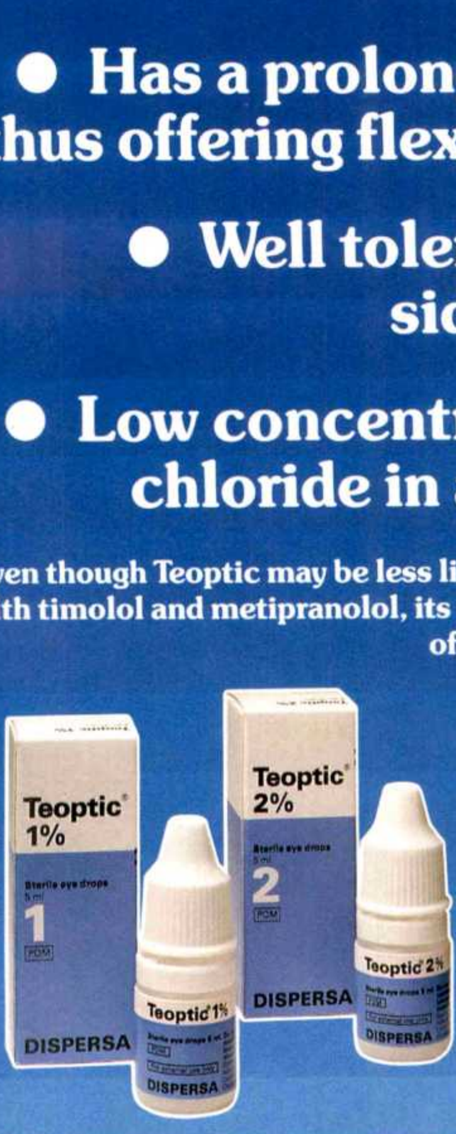
1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10,** 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85,** 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105,** No.2, 150-154.

Teoptic: Abbreviated prescribing information
Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity: **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

- Effectively lowers IOP[1]
- Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol *[2,3]
- Has a prolonged therapeutic effect[4] thus offering flexible b.d. dosage regimen
- Well tolerated with few local side-effects[5]
- Low concentration of benzalkonium chloride in a buffered solution.

* Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.



Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.
Teoptic is under licence from Otsuka, Japan.

Further information is available on request to the above address.

Fucithalmic
fusidic acid
Contains Fucidin fusidic acid
twice daily for bacterial conjunctivitis

▼ Prescribing Information.
Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses**: Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications**: Bacterial conjunctivitis due to sensitive organisms. **Dosage**: One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications**: Hypersensitivity to any component. **Precautions**: Should not be used when contact lenses are being worn. **Side effects**: Transient stinging. Hypersensitivity may occur. **Product Licence Number**: 0043/0137. **Basic N.H.S. Price**: £2.25/5g tube.

Further information available on request:

Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

British Journal of Ophthalmology, 1990, 74, 393–399

Variation in epiretinal membrane components with clinical duration of the proliferative tissue

I Morino, P Hiscott, N McKechnie, I Grierson

Abstract

Immunohistochemical investigations were conducted on surgically excised epiretinal membranes to determine how cellular and extracellular components of proliferative vitreoretinopathy membranes change with time. Specimens of less than four months' duration contained a significantly higher proportion of retinal pigment epithelial cells than later membranes. No association was found between membrane duration and the content of collagen subtypes I to IV and laminin, but 'early' specimens contained significantly more fibronectin than did 'late' membranes. Fibronectin and collagens I, III, and IV showed a variable relationship with glial cells and were most consistently associated with retinal pigment epithelial and fibroblast-like cells. These observations may explain some of the surgical features of epiretinal membranes.

Epiretinal membranes (ERMs) are fibrocellular proliferations on the retinal surface whose content depends on several factors including aetiology and clinical duration. Thus ERMs complicating rhegmatogenous retinal detachment – that is, proliferative vitreoretinopathy (PVR) membranes – contain retinal pigment epithelial (RPE) cells, while membranes arising in the absence of a retinal hole tend to lack RPE.[1] Furthermore, long standing ERMs contain more collagen but fewer cells than membranes of short clinical duration.[2,3] Although the association between clinical duration and ERM fibrosis is reminiscent of the scarring process in the skin, unlike dermal wounds[4] little is known about the effect of aging on specific cellular or extracellular ERM elements.

To determine how subcomponents of ERMs change with time we have undertaken an immunohistochemical study of (1) various subpopulations of cells (including glia and RPE) and extracellular matrix constituents (collagen types I to IV and the glycoproteins fibronectin and laminin) in surgically excised specimens, and (2) a correlation between the cellular and extracellular components of the membranes. We restricted this investigation to PVR membranes (to minimise the effects of aetiological factors on membrane content).

Department of Pathology, Institute of Ophthalmology, London
I Morino
P Hiscott
N McKechnie
I Grierson

Correspondence to:
Paul Hiscott, Department of Pathology, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT

Accepted for publication
2 February 1990

Materials and methods

Twenty ERMs were obtained during closed pars plana microsurgery for PVR (grade C1 or worse[5]). The ERMs were arbitrarily grouped into those of less than four months' duration (early ERMs) and those over four months' duration (late ERMs).

Specimens were processed for immunohistochemistry as previously described.[3,6-8] Serial sections were cut right through the specimens and immunostained sequentially with a panel of monoclonal antibodies and polyclonal antisera to the following cellular intermediate filaments or extracellular matrix components:

(i) glial fibrillary acidic protein (GFAP) – a glial cell marker (mouse monoclonal anti-GFAP, ICN Biomedical);

(ii) cytokeratins – an epithelial marker (mouse monoclonal antibodies, NCL 5D3 Euro-Diagnostics and K_G8·13 SIGMA);

(iii) collagen type I – interstitial collagen also found in maturing scars (goat antiserum, Southern Biotechnology Associates);

(iv) collagen type II – the collagen of the vitreous (goat antiserum, Southern Biotechnology Associates);

(v) collagen type III – interstitial collagen also found in early scars (goat antiserum, Southern Biotechnology Associates);

(vi) collagen type IV – a component of basement membranes (goat antiserum, Southern Biotechnology Associates);

(vii) fibronectin – a glycoprotein which has important roles in healing wounds (rabbit antiserum, DAKOPATTS);

(viii) laminin – a glycoprotein fraction of basement membranes (rat monoclonal antibody, ICN Biomedical).

Where the specimens were too small to provide sufficient sections for all the immunostaining procedures, the specimen was discarded from the study.

Appropriate positive and negative controls were applied to all procedures.[3,6,7] In addition some sections were stained with haematoxylin and eosin. The preparations were examined by bright field, differential interference contrast, and epifluorescence microscopy.

The percentage of cells staining positively for GFAP and cytokeratin together with the proportion of the tissue staining for collagen types I to IV, fibronectin and laminin was recorded for each specimen (this semiquantitative assessment was made by three observers independantly and the results subsequently averaged).[3,7] For statistical comparisons between early and late ERMs the Mann-Whitney U test was adopted (level of significance taken as $p<0·05$).

Relationships between the cellular and extracellular components of the specimens were recorded from comparisons of immunostained sequential ERM sections. Both intra- and extracellular collagens and glycoproteins may show immunoreactivity,[3,9] but we did not attempt to quantitate immunolabelling at either of these sites.

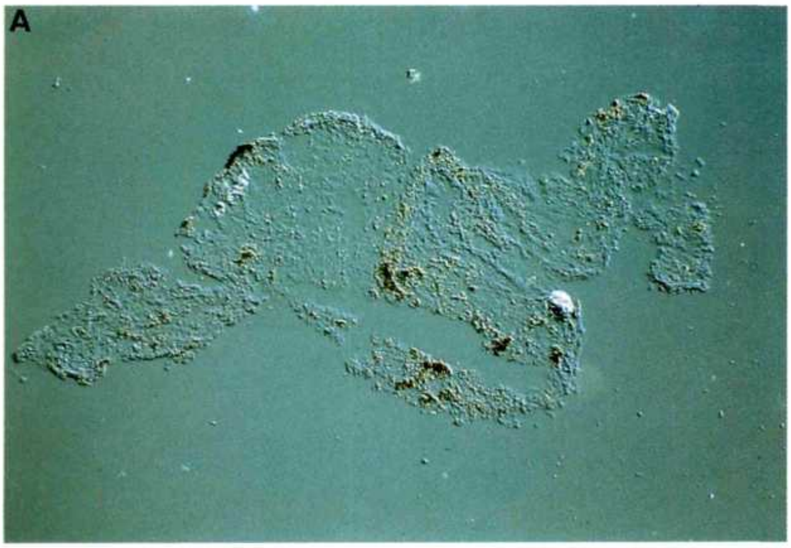


Fig 1A

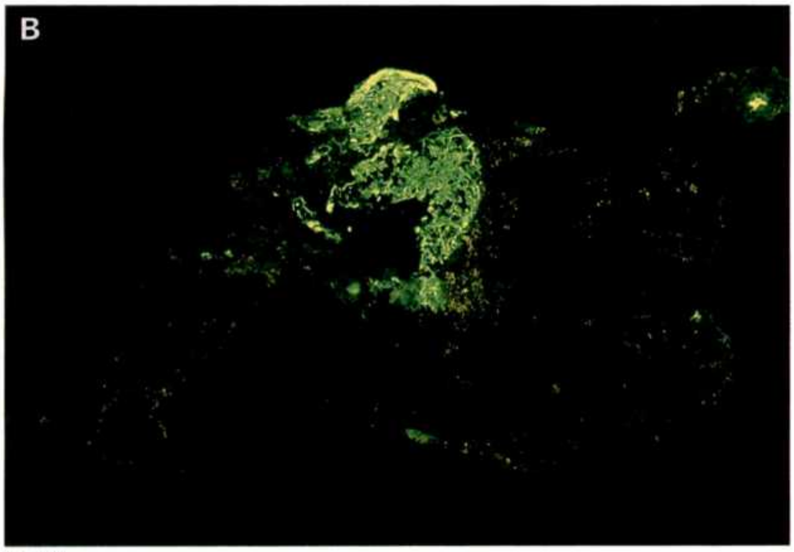


Fig 1B

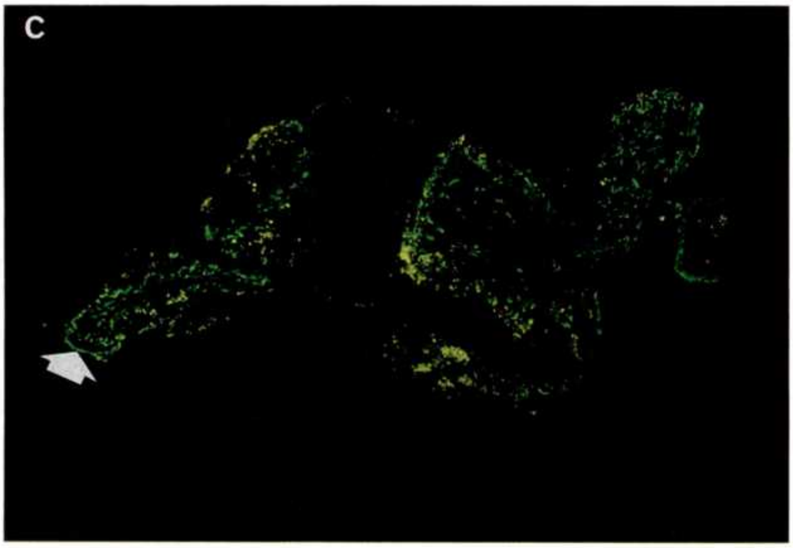


Fig 1C

Figure 1: (A) Differential interference contrast micrograph and (B) and (C) epifluorescence micrographs of serial sections from an early epiretinal membrane. (A) The general morphology of the tissue can be seen, including deposits of brown melanin granules. (B) Immunofluorescence stain for GFAP. A large focus of glial cells is present in the centre of the section. (C) Immunofluorescence stain for cytokeratin. Many cytokeratin-positive cells are present in the non-glial part of the tissue, including a layer of cells (arrow). (All ×60).

TABLE I *Cellular components of epiretinal membranes (ERMs)*

ERM no.	*GFAP-positive cells*	*Cytokeratin-positive cells*
(A) Early membranes (≤ 4 months)		
1	20%	30%
2	15%	40%
3	20%	40%
4	20%	15%
5	10%	15%
6	10%	30%
7	5%	40%
*8	20%	5%
9	10%	30%
(B) Late membranes (>4 months)		
10	60%	20%
11	30%	40%
12	20%	10%
13	5%	20%
14	0%	5%
15	20%	10%
16	30%	10%
*17	15%	0%
18	15%	5%
19	40%	0%
20	10%	0%

GFAP=glial fibrillary acidic protein.
*Vascular component in membrane.

Results

CELLULAR COMPONENTS OF ERMs

GFAP-positive cells were observed in 19 of the 20 ERMs (Table I, Figs 1 to 3). Although late membranes appeared to contain proportionally more glial cells (22%) than early ERMs (14%), there was no significant difference between the two groups. The cells varied in shape. They included stellate and rounded cells, and were usually arranged in foci or layers (layers or foci were present in eight early and nine late ERMs), only occasionally being seen as isolated cells at the edge of the tissue or on strips of inner limiting lamina (ILL) of the retina (Figs 1 to 3).

Seventeen of the ERMs contained cytokeratin-positive cells (Table I, Figs 1, 4, 5). All the early membranes had an epithelial cell component (with an average of 27% RPE cells each), while eight of the 11 late membranes incorporated RPE cells (average content 11%), and the difference was significant ($p<0.02$). Eight early and five late ERMs contained rounded or cuboidal RPE cells arranged in foci or layers (Table I, Figs. 1, 4, 5), while all of the early and four of the late specimens contained elongated, sometimes plump or spindle-shaped ('fibroblast-like') cytokeratin-positive cells set in fibrous tissue (Figs. 1, 4).

GFAP- and cytokeratin-negative cells were present in all ERMs (Figs. 1 to 5), but no significant difference was found between the proportions of these cells in early (59%) and late (66%) specimens. Apart from vascular endothelial cells (two ERMs, Table I), the non-glial, non-epithelial cells comprised inflammatory and elongated, fibroblastic ('true fibroblast') GFAP- and cytokeratin-negative cells. These cells generally were distributed in the fibrous component of the membranes.

EXTRACELLULAR COMPONENTS

Collagen types I, III, and IV were present in all specimens (Table II, Figs 2 to 5). while 14 ERMs were immunoreactive for collagen type II.

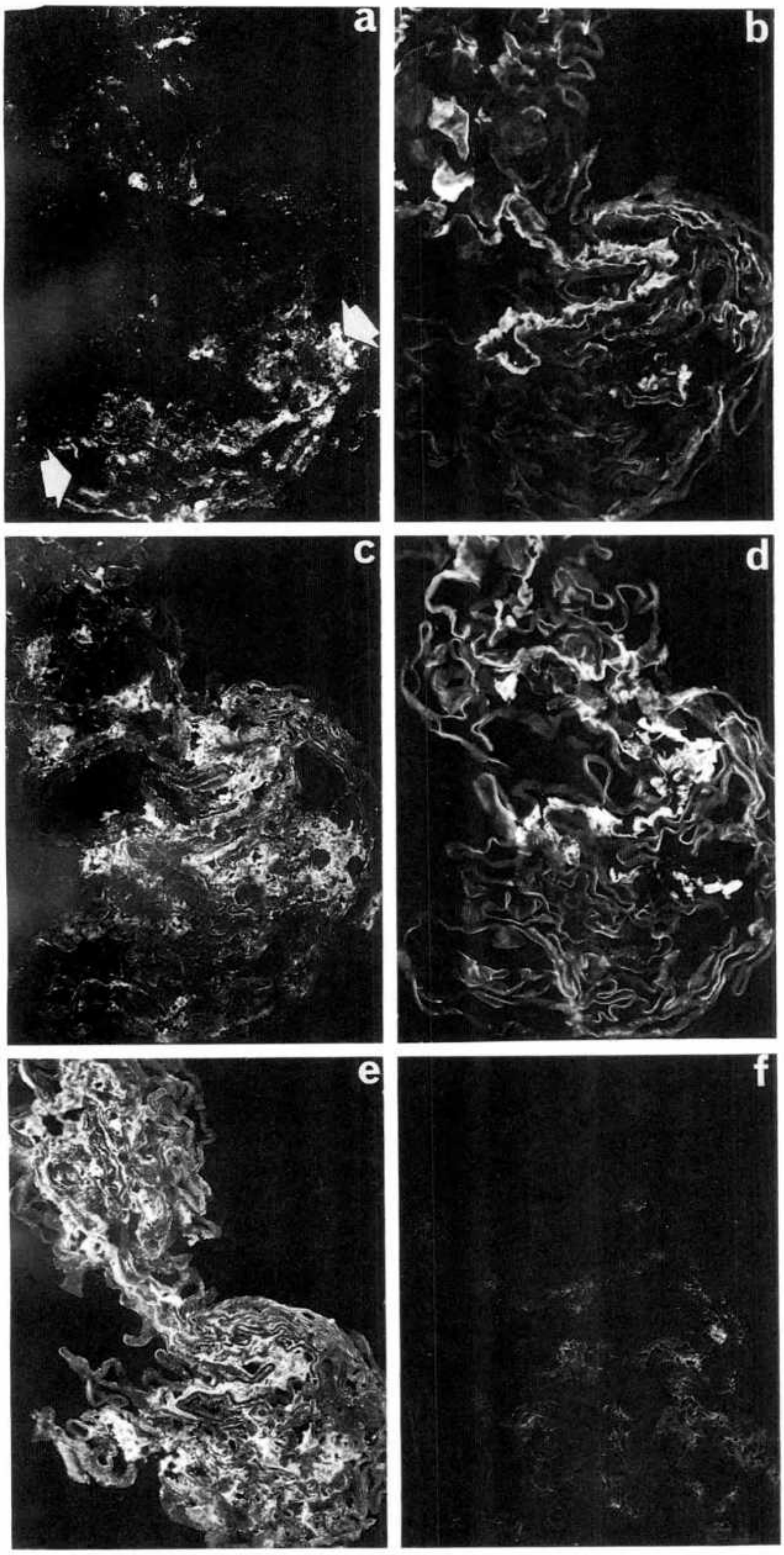


Figure 2: Epifluorescence micrographs of serial sections from a late ERM.
(a) Immunostaining for GFAP reveals glial cells (arrows). (b), (c), and (d). Immunolabelling for collagen types I, II and IV respectively show that much of the specimen consists of thick, ILL-like material (seen by type IV collagen immunoreactivity in d). The ILL and glial components are associated with the collagen subtypes. (e) and (f): Immunostained for fibronectin and laminin respectively. Fibronectin is abundant in the specimen while laminin is a relatively minor element of the tissue. (All × 165).

TABLE II *Extracellular components of epiretinal membranes (ERMs)*

ERM no.	I	II	III	IV	FN	LM
(A) Early membranes (≤4 months)						
1	60%	5%	60%	45%	95%	0%
2	80%	0%	70%	55%	75%	0%
3	60%	5%	60%	45%	70%	5%
4	80%	15%	80%	80%	85%	15%
5	70%	10%	70%	65%	85%	5%
*6	60%	5%	65%	90%	95%	10%
7	85%	20%	85%	65%	80%	10%
8	80%	15%	75%	70%	90%	20%
*9	55%	0%	55%	75%	65%	5%
(B) Late membranes (>4 months)						
10	35%	0%	35%	25%	25%	0%
*11	30%	30%	25%	60%	55%	30%
12	80%	5%	80%	70%	90%	0%
13	90%	20%	90%	55%	65%	10%
14	70%	0%	70%	55%	50%	10%
15	80%	0%	80%	75%	95%	5%
16	70%	5%	70%	50%	60%	10%
17	70%	10%	70%	25%	65%	5%
18	85%	0%	85%	65%	15%	5%
19	60%	5%	60%	25%	55%	0%
20	90%	15%	90%	20%	90%	0%

I to IV = collagen types I to IV.
FN = fibronectin.
LM = laminin.
*Membranes with abundant inner limiting lamina.

Although early ERMs appeared to contain more collagen type IV than late membranes, no statistical difference could be demonstrated between the proportion of any of the individual collagen types in the two groups. However, types I and III were the most abundant forms of collagen in the specimens, while collagen type II was a minor component ERMs. (The content of type IV collagen was intermediate between types I/III and II.) The distributions of collagen types I and III were similar and showed confluent areas of immunoreactivity which in some cases occupied almost the entire specimen (Table II, Fig 5). Type II collagen tended to represent small isolated areas in the specimens, frequently adjacent to the specimen edge or ILL (Fig 2c). Type IV collagen also formed confluent areas and was only found in association with collagen types I and III or ILL (Fig 2, 4).

Although all the specimens contained fibronectin (Table II, Figs 2, 5), the glycoprotein was more abundant in early than late ERMs, and the difference was significant ($p<0.038$). Fibronectin was distributed in focal patches or evenly throughout large areas of the tissues.

Laminin was present in 14 of the 20 ERMs, but was a minor component in the tissue (Table II, Figs 2, 5). Although all but two early membranes contained laminin while four late specimens lacked the glycoprotein, no significant difference was found between the overall laminin content of early and late groups. The ILL showed the most consistent laminin immunolabelling, though this tended to be patchy. Laminin was sometimes distributed as small isolated foci adjacent to cells in collagen or around ILL (Fig 2).

RELATIONSHIP BETWEEN CELLULAR AND EXTRACELLULAR ERM COMPONENTS

GFAP-positive cells showed variable immunoreactivity for extracellular matrix components (within and between ERMs – Fig 2, 3). In four ERMs (two early and two late) glia showed uniform immunostaining for collagen subtypes I, III, and IV (Figs 3a, b). However, commonest staining pattern for collagen I, III, and IV in glia was of some collagen-positive cells in a predominantly collagen-negative glial component; approximately half (four early and four late) the

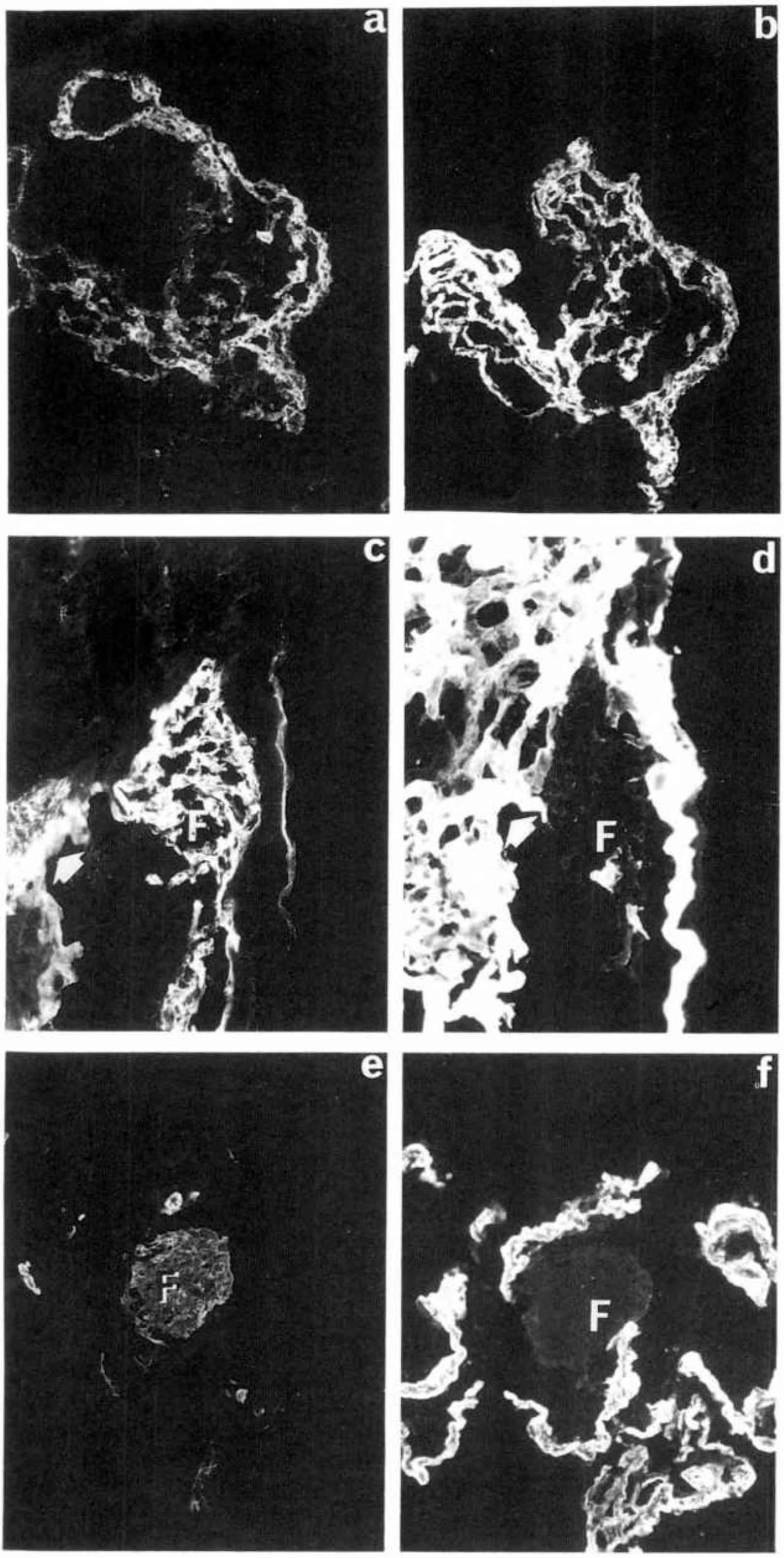


Figure 3: Epifluorescence micrographs of epiretinal membranes stained with the immunofluorescence technique. (a) An early ERM stained for GFAP shows a layer of glial cells which are intensely immunoreactive for (b) collagen type III (×125). (c) Another early membrane stained for GFAP contains a focus (F) and a layer (arrow) of glial cells. (d) A sequential section of the membrane shown in (c) has been labelled for collagen type I to demonstrate that the glial layer (arrow) stains for the collagen subtype, while the glial focus (F) is predominantly collagen type I-negative (×250). (e) and (f): Sequential sections from a late ERM stained for (e) GFAP and (f) collagen type III. A focus of glial cells (F) does not immunoreact for collagen type III, while the surrounding non-glial shows intense labelling (× 125).

membranes displayed this patchy pattern. In two specimens glial layers immunolabelled for collagen types I, III, and IV while glial foci were largely collagen-negative (Fig 3c, d). The glial cells in the remaining specimens (two early, three late) did not immunoreact for collagen types I, III, or IV (Fig 3e, f). Collagen type II immunostaining correlated with a few glial cells in one early and three late ERMs, being most pronounced where glia were adjacent to ILL strips (Fig 2). Fibronectin was associated with glial cells in 15 membranes (Fig 2). Fibronectin-positive cells were uniformly distributed in the glial component of six early and three late ERMs, while in the rest of the specimens the glial cells displayed patchy staining for the glycoprotein. Glial cells showed patchy laminin immunoreactivity in three early and four late ERMs, often adjacent to ILL (Fig 2).

Rounded or cuboidal RPE cells in all but one ERM showed uniform immunoreactivity for collagen types I, III, and IV (Fig 4 , 5), the exception being a late membrane in which the collagen subtypes were largely restricted to a layer round an RPE cell focus (Fig 4e, f). Patchy collagen type II staining coincided with cuboidal RPE in four early and three late ERMs. Fibronectin colocalised with all cuboidal RPE in the ERMs (Fig 5) and was uniformly distributed in the cuboidal RPE of seven early and one late specimen. Patchy laminin immunoreactivity coincided with cuboidal RPE in five of the early and three of the late specimens.

Cytokeratin-positive fibroblast-like cells showed uniform colocalisation of collagen types I and III and, in all but two late ERMs which showed patchy labelling, collagen type IV (Fig 4). By contrast, collagen type II was associated only with fibroblast-like RPE cells in four early and two late specimens, and then chiefly in a patchy distribution. All fibroblast-like RPE showed fibronectin immunoreactivity, with a uniform staining pattern, in eight early and two late ERMs. Fibroblast-like RPE showed either patchy (in one early and two late membranes) or no labelling for laminin.

Cytokeratin-negative fibroblasts showed uniform colabelling for collagen types I, III, and IV in all early ERMs and six late ERMs (Fig 5), while in four late membranes these cells displayed uniform staining for collagen I and III but patchy immunoreactivity for collagen IV. The fibroblasts in one late ERM demonstrated patchy collagen I, III, and IV labelling. Uniform collagen type II staining was associated with fibroblasts in only one (early) specimen and patchy labelling in two early and three late ERMs. The fibroblasts in all ERMs were associated with fibronectin, and the fibroblasts in eight early together with five late specimens showed a uniform immunoreactivity to the glycoprotein (Fig 5). Laminin was associated with the fibroblasts of none of the early and three of the late ERMs (in a patchy distribution).

Discussion

Our semiquantitative immunohistochemical study of PVR membranes supports the concept that glial cells persist in longstanding ERMs.[3] ERMs also could contain glial elements avulsed from the retina during surgical removal.[6,10] However, surgically excised membranes and ERMs 'in situ' (that is, in enucleated globes)

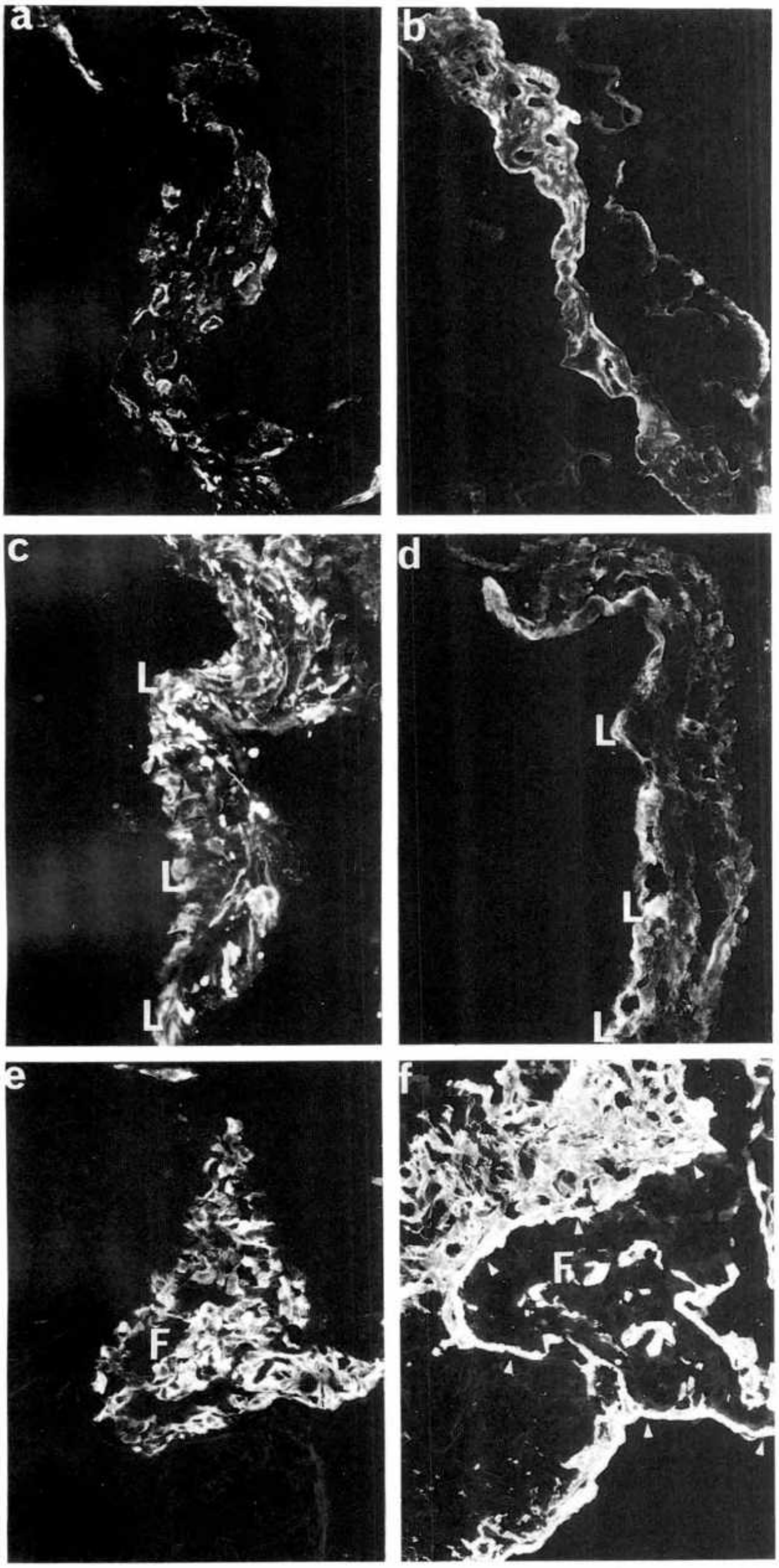


Figure 4: Epifluorescence micrographs of ERMs stained with the immunofluorescene method. (a) An early membrane stained for cytokeratin contains abundant epithelial cells, while (b) a serial section shows the epithelial cells are associated with collagen type I immunoreactivity (× 330). (c) and (d): Serial sections of an early ERM stained for (c) cytokeratin to reveal a layer of cuboidal epithelial cells (L) adjacent to fibrous tissue containing numerous elongated and plump epithelia. The serial section (d) has been stained for collagen type IV to show that both the layered, cuboidal (L) and fibroblast-like epithelial cells immunoreact for the collagen subtype (x330). (e) A late membrane, stained for cytokeratin, contains a focus of RPE cells (F) which shows immunoreactivity for collagen type I (f) is chiefly restricted to a layer (arrowheads) around the RPE focus (F; ×330).

have similar distributions of GFAP-positive cells.[6] Nevertheless, the finding of a slightly larger proportion of glial cells in late ERMs than in early membranes is most likely due to a decline in other cell numbers and probably does not represent a time-dependant increase in total glial cells.

Conversely, late ERMs contained relatively fewer cytokeratin-positive cells than early ERMs. This finding was unexpected, since previous investigations revealed aggregated RPE in late as well as early ERMs'[3] and developing PVR membranes accrue S100 positive cells.[11] However, S100 is present in a variety of cells[12,13] whereas cytokeratins are thought to be specific for epithelial cells. Moreover, cytokeratin-positive fibroblast-like cells are present in the fibrous component of the ERMs[7,8] and the present study shows that these fibroblast-like RPE are present in all the early but only a few of the late membranes. Therefore the fibroblast-like subpopulation of RPE may be specifically lost in aging, though there is also some decline in aggregated RPE.

The age related decline in RPE may in part explain the differences between two previous studies of cytokeratin-positive cells in ERMs. An investigation at this laboratory[7] found that not all PVR membranes contained RPE, whereas Jerdan and colleagues[14] found RPE in all their PVR specimens. If the specimens examined by Jerdan and coworkers were of a clinically shorter duration than those of our earlier study the differences might have been expected, since in this investigation all the early ERMs contained RPE cells, and cytokeratin-positive cells were absent only from some longstanding PVR membranes. Although we did restrict the specimens in our earlier study to predominantly cellular ERMs,[7] we did not attempt to group them according to clinical duration.

The late ERMs of this investigation contained approximately the same percentage of GFAP- and cytokeratin-negative cells as did early membranes. Previous investigations revealed that late ERMs tended to contain relatively more inflammatory cells than early specimens, while cells with the morphological features of fibroblasts underwent lipoidal degeneration.[3] The fibroblastic cells, which probably included fibroblast-like RPE, may have been deprived of nutritional requirements following their 'entombment' in extracellular material.

Our findings concerning the extracellular content of ERMs generally are in keeping with previous immunochemical studies of PVR specimens.[3,10,11,14-16] Thus the ERMs usually contain abundant collagen types I and III and fibronectin, while, except in association with fragments of ILL, laminin and collagen II/IV immunoreactivity is more variable. No difference in the proportions of any collagen subtype or laminin is apparent between the two 'age' groups, though some correlation between ERM duration and collagen subtype might be expected, because mature dermal wounds contain more collagen type I than type III. The persistence of type III collagen in late ERMs may indicate protracted synthesis of extracellular matrix components within the epiretinal tissue. However, late ERMs do contain less fibronectin than early specimens. A time dependant change in fibronectin is also seen in healing wounds, where the glycoprotein has important adhesive

P 25,369

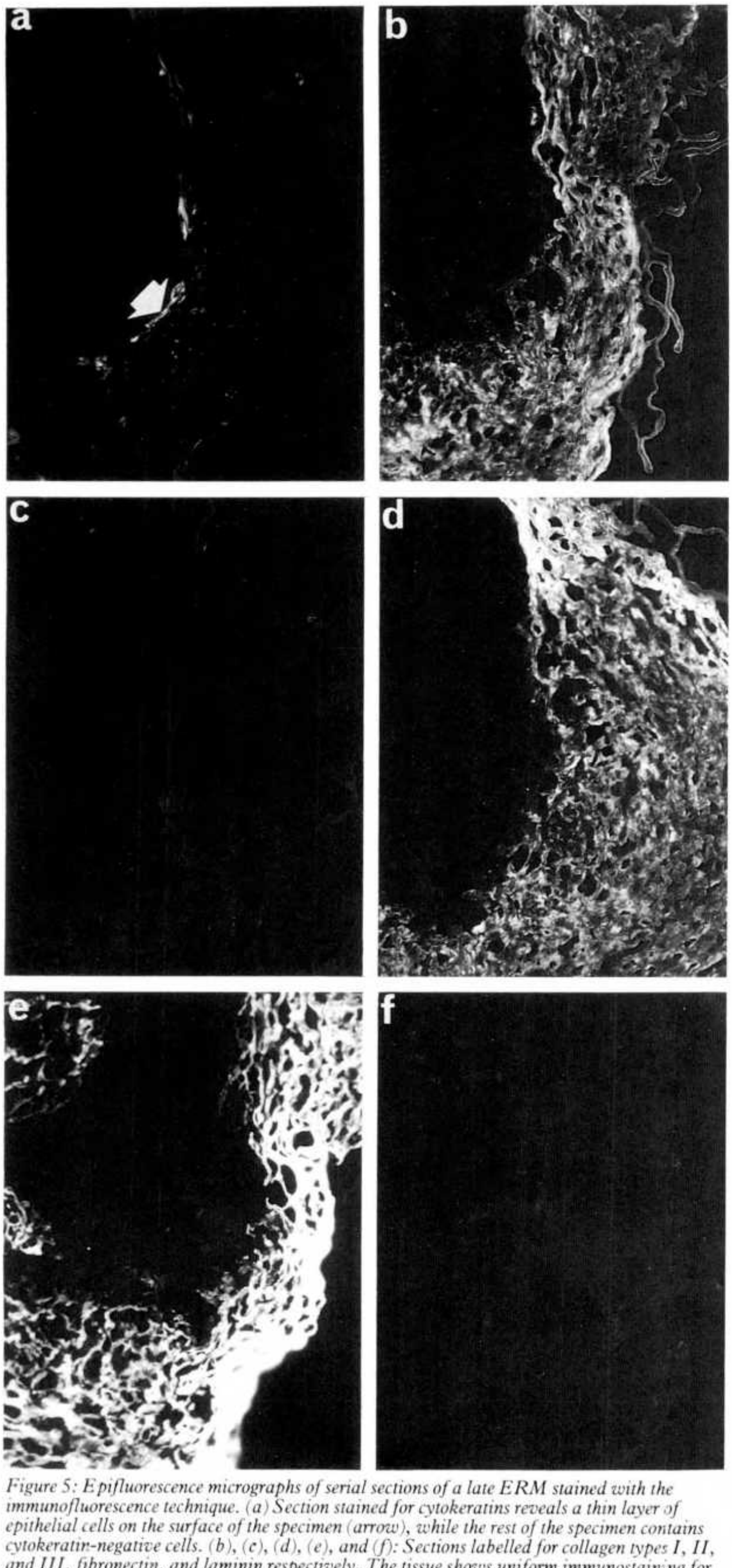


Figure 5: Epifluorescence micrographs of serial sections of a late ERM stained with the immunofluorescence technique. (a) Section stained for cytokeratins reveals a thin layer of epithelial cells on the surface of the specimen (arrow), while the rest of the specimen contains cytokeratin-negative cells. (b), (c), (d), (e), and (f): Sections labelled for collagen types I, II, and III, fibronectin, and laminin respectively. The tissue shows uniform immunostaining for collagen types I and III and fibronectin, but no collagen type II or laminin reactivity. (All × 165).

roles in the early stages, but as the scar matures fibronectin disappears.[17-19] The reduction of bioadhesive fibronectin with aging may be a factor in explaining why long-standing ERMs are more easily dissected than early membranes.[20]

CORRELATION BETWEEN CELLULAR AND EXTRACELLULAR ERM COMPONENTS

A recent immunohistochemical investigation indicates that collagen in PVR membranes is not produced by glial cells.[11] However, glial cells can produce collagen in vitro and in the vitreous of rabbits,[21] while non-vitreous collagen may be found in ERMs whose cellular content is glia in origin.[22,23] Although the synthetic activities of cells in ERMs cannot be inferred from their immunoreactivity to various extracellular matrix constituents alone, our observation of glial cells showing variable immunoreactivity for extracellular matrix components in PVR specimens is in keeping with the idea that in some circumstances epiretinal glia synthesises collagens and glycoproteins.

By contrast, the consistent immunoreactivity for collagen types I, III, and IV shown by RPE cells, including fibroblast-like forms, provides further evidence for the concept that part of the collagen of ERMs – at least in PVR – is produced by RPE cells.[11,14,24] Moreover, cytokeratin-negative fibroblast-like cells in ERMs also show a particular association with collagen types I and III, in keeping with the view that, as in dermal wounds, the fibroblastic cells are synthesisers of extracellular matrix. Thus the findings suggest that several cell types are responsible for the ERM fibrous component. Nevertheless, the colocalisation of extracellular material constituents and ERM cells may be due to several factors – including the migration of the cells into a pre-existing scaffold. Cellular migration may explain the variable relationship between basement membrane components and fibroblastic cells.

The combination of fibroblastic cells and extracellular material provides a fibrous ERM portion which often lies adjacent to a layer of glial cells, or sometimes RPE cells, and gives many of the ERMs a laminated architecture. This organisation of membrane components underlies the care required to ensure all lamellae are removed during ERM 'peeling',[20] since a surgical cleavage plane may form between the layers of epiretinal tissue. Moreover, as the ERM matures, planes between lamellae may be accentuated by the decline in fibronectin.

We thank Mr C Canning, Mr R Cooling, Mr Z Gregor, Mr P Leaver, and Professor D McLeod, who provided many of surgical specimens. Dr D Minassian assisted with the statistical analyses. Our work has been funded by the Wellcome Trust (grant no. 17095/1.4R) and Fight for Sight.

1 Kampik A, Kenyon KR, Michels RG, Green WR, de la Cruz Z. Epiretinal and vitreous membranes: comparative study of 56 cases. *Arch Ophthalmol* 1981; **99**: 1445–54.
2 Constable IJ, Tolentino FI, Donovan RH, Schepens CL. Clinico-pathologic correlation of vitreous membranes. In: Pruett RD, Regan DJ, eds. *Retinal congress*. New York: Appleton-Century-Crofts, 1974; 245–57.
3 Hiscott PS, Grierson I, McLeod D. Natural history of fibrocellular epiretinal membranes: a quantitative, autoradiographic and immunohistochemical study. *Br J Ophthalmol* 1985; **69**: 810–23.
4 Peacock EE. Inflammation and the cellular response to injury. *Wound repair*. Philadelphia: Saunders, 1984: 1–14.
5 The Retina Society Terminology Committee. The classification of retinal detachment with proliferative vitreoretinopathy. *Ophthalmology* 1983; **90**: 121–5.
6 Hiscott PS, Grierson I, Trombetta CJ, Rahi AH, Marshall J, McLeod D. Retinal and epiretinal glia–an immunohistochemical study. *Br J Ophthalmol* 1984; **68**: 698–707.
7 Hiscott PS, Grierson I, McLeod D. Retinal pigment epithelial cells in epiretinal membranes: an immunohistochemical study. *Br J Ophthalmol* 1984; **68**: 708–15.

8 McKechnie NM, Boulton M, Robey H, Savage FJ, Grierson I. The cytoskeletal elements of human retinal pigment epithelium: in vitro and in vivo. *J Cell Sci* 1988; 91: 303–12.

9 Newsome DA, Pfeffer BA, Hewitt AT, Robey PG, Hassell JR Detection of extracellular matrix molecules synthesized in vitro by monkey and human retinal pigment epithelium influence of donar age and multiple passages *Exp Eye Res* 1988, 46: 305–21.

10 Sramek SJ, Wallow IH, Stevens TS, Nork TM Immunostaining of preretinal membranes for actin, fibronectin and glial fibrillary acidic protein. *Ophthalmology* 1989; 96: 835–41.

11 Ihme A, Tavakolian U, Pham-Duy TH, Wollensak J Characterisation of cell types in vitrectomy specimens by immunohistochemical methods. In: Heimann K, Wiedemann P, eds. *Proliferative Vitreoretinopathy*. Heidleberg: Kaden, 1989: 73–7.

12 Crocker J, Jenkins R, Campbell J, Fuggle WJ, Shah VM Immunohistochemical demonstration of S-100 protein in salivary gland neoplasms. *J Pathol* 1985; 146: 115–21

13 Dwarakanath S, Lee AKC, Delellis RA, Silvermann ML, Frasca L, Wolfe HJ S-100 protein positivity in breast carcinomas: a potential pitfall in diagnostic immunohistochemistry *Hum Pathol* 1987; 18: 1144–8.

14 Jerdan JA, Pepose JS, Michels RG, Hayashi H, de Bustros S, Sebag M, Glaser BM. Proliferative vitreoretinopathy membranes, an immunohistochemical study *Ophthalmology* 1989; 96: 801–10.

15 Scheiffarth OF, Kampik A, Gunther H, von der Mark K. Proteins of the extracellular matrix in vitreoretinal membranes *Graefes Arch Clin Exp Ophthalmol* 1988, 226: 357–61.

16 Scheiffarth OF, Kampik A, Gunther-Koszka H, von der Mark K Collagens, fibronectin and laminin in proliferative vitreoretinopathy. In Heimann K, Wiedemann P, eds *Proliferative Vitreoretinopathy* Heidleberg. Kaden, 1989: 134–8

17 Kurkinen M, Vaheri A, Roberts PJ, Stenman S Sequential appearance of fibronectin and collagen in experimental granulation tissue. *Lab Invest* 1980, 43: 47–51

18 Yamada KM, Yamada SS, Pastan I The major cell surface glycoprotein of chick embryo fibroblasts is an agglutinin *Proc Natl Acad Sci USA* 1975; 72. 3158–62

19 D'Ardenne AJ, McGee JO'D Fibronectin in disease *J Pathol* 1984; 142: 235–51.

20 McLeod D, Hiscott PS, Grierson I Age-related cellular proliferation at the vitreoretinal juncture *Eye* 1987, 1: 263–81.

21 Burke JM, Kower HS Collagen synthesis by rabbit neural retina in vitro and in vivo. *Exp Eye Res* 1980, 31. 213–26

22 Kenyon KR, Pederson JE, Green WR, Maumenee AE. Fibroglial proliferation in pars planitis. *Trans Ophthalmol Soc UK* 1975; 95: 391–7.

23 Rentsch FJ. The ultrastructure of preretinal macular fibrosis. *Graefes Arch Clin Exp Ophthalmol* 1977, 203: 321–37.

24 Machemer R, van Horn D, Aaberg TM Pigment epithelial proliferation in human retinal detachment with massive periretinal proliferation *Am J Ophthalmol* 1978; 85. 181–91

British Journal of Ophthalmology, 1990, 74, 400–404

Hypoxic viscosity and diabetic retinopathy

T Rimmer, J Fleming, E M Kohner

Abstract

Diabetic and sickle retinopathy have features in common – for example, venous dilatation, microaneurysms, and capillary closure preceding neovascularisation. Bearing in mind that haemoglobin in poorly controlled diabetes is abnormal and that extremely low oxygen tensions (known to cause sickling) exist in the healthy cat retina, we wished to explore the possibility that diabetic blood, like that of sickle cell disease, may become more viscous when deoxygenated. To do this we measured whole blood viscosity, under oxygenated and deoxygenated conditions, of 23 normal persons, 23 diabetic patients without retinopathy, and 34 diabetic patients with retinopathy. The shear rate used was 230 s^{-1}, which is similar to that thought to prevail in the major retinal veins. The viscosity of blood from normal persons, corrected for packed cell volume, did not change significantly on deoxygenation: mean 4·54 (SD 0·38) cps, versus, 4·57 (0·39) paired *t* test, $p=0.66$. Similarly the blood from diabetics without retinopathy showed no change: 4·42 (0·45) versus 4·42 (0·30), $p=0.98$; whereas the blood from patients with retinopathy changed from 4·82 (0·48) to 4·95 (0·63), $p=0.027$. The hypoxic viscosity ratio (deoxygenated divided by oxygenated viscosity) correlated with total serum cholesterol ($r=0.44$, $p=0.018$) but not with HbA1, serum glucose, triglycerides, or age. A disproportionate increase in venous viscosity relative to arterial viscosity would lead to increased intraluminal and transmural pressure and therefore exacerbate leakage across capillary walls.

Department of Medicine, Royal Postgraduate Medical School, London W12 0HS
T Rimmer
E M Kohner

Department of Surgery
J Fleming

Correspondence to:
Timothy Rimmer, FRCS,
Biomedical Engineering Department,
Northwestern University,
Evanston, Illinois 60208,
USA.

Accepted for publication 15 February 1990

Diabetic retinopathy is the commonest cause of blindness in the working age group in England[1] and the United States.[2] Since its pathophysiology is still not understood, all possible factors should be explored. We considered the well known fact that diabetic retinopathy has features in common with sickle cell retinopathy, namely, venous dilatation, microaneurysms, and capillary closure[3] preceding neovascularisation,[4] even though the new vessels are usually in different areas.

Both diseases are also characterised by abnormal levels of different haemoglobin components, which in sickle cell disease, under conditions of hypoxia, cause a marked rise in viscosity. Even in health the functional reserve of oxygen of the human retina lasts only seconds,[5] and the oxygen tension (in cats) just proximal to the outer nuclear layer has been shown to be 12 mmHg[6] and even zero,[7] and the PO_2 of blood in human retinal veins has recently been estimated to be as low as 25 mmHg.[8] If low oxygen tensions interfere with blood flow anywhere, it is likely to happen in the retina. Venous dilatation, one of the first clinical signs of diabetic retinopathy, could be the result of the blood becoming more viscous as it enters the venous side of the circulation. The aim of this study was to test the hypothesis that blood from diabetic patients becomes more viscous under conditions of extreme hypoxia such as are thought to exist even in the healthy retina.

Patients and methods

PATIENTS

Consecutive patients were entered into the study from the Diabetic Retinopathy and General Diabetic Clinics of the Hammersmith Hospital. The 57 patients in the study were later grouped, from clinical records and reference to fundus photographs, according to the retinopathy status of the worse eye: 23 had no retinopathy, 11 had background retinopathy (at least one microaneurysm but no macular oedema nor preproliferative changes), nine had more severe background retinopathy with exudative maculopathy (one also having cotton-wool spots), and 14 had previously undergone argon laser panretinal photocoagulation (at least 2000 burns 500 μm in size and strong enough to cause moderate blanching) for proliferative retinopathy. No patients in the study had active proliferative retinopathy. Twenty-three normal subjects were recruited from staff and relatives of patients. The details of patients and controls are shown in Table I.

Methods

After informed consent was obtained, blood samples were collected from the antecubital vein in lithium heparin containers (15 IU/ml). The samples were collected from five subjects at a time. From each sample 1·5 ml was transferred to each of two 10 ml syringes, which were immediately capped. There were five syringes containing blood to be equilibrated with an oxygenating gas mixture and five syringes containing blood to be equilibrated with a deoxygenating gas mixture. A frame was constructed which allowed five syringes of blood/gas to be equilibrated simultaneously.

TABLE I *Details of patients and normal persons*

	Number	*Age (yr)**	*Duration of diabetes (yr)*
Normal	23	38·5 (15·5)	–
No retinopathy	23	55·7 (15·0)	7·7 (6·0)
Background	11	53·7 (15·2)	9·7 (4·2)
Maculopathy	10	55·1 (8·2)	12·1 (5·4)
Postphotocoagulation	14	50·1 (11·5)	16·1 (10·9)

* Means (with standard deviations)

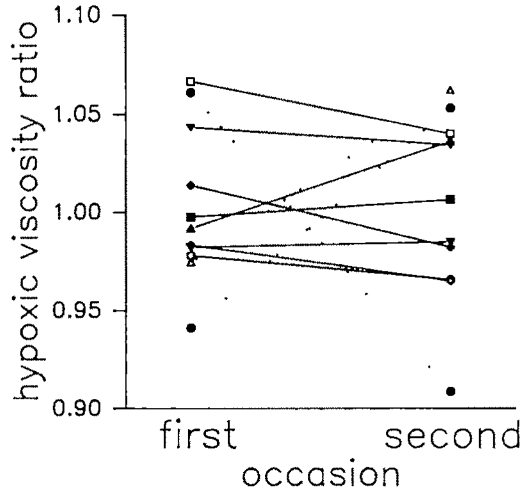


Figure 1: Reproducibility of the hypoxic viscosity ratio (deoxygenated divided by oxygenated viscosity) of 11 normal subjects, the two measurements being several weeks apart and both at the shear rate of 230 s^{-1}. The solid lines represent reproducibility scores greater than 95%, whereas the dotted lines represent those between 84 and 95%.

The oxygenating gas mixture was 95% air/5% CO_2 by volume and the deoxygenating mixture 1·4% 0_2/7·0% CO_2/balance N_2. . Both gas mixtures were passed through a humidifyer (Sintaglass Ltd, London) before being exposed to the blood samples. The first five syringes containing blood samples were deoxygenated by filling the remaining 8·5 ml of the syringes with the appropriate gas mixture and then rotating the syringes at approximately 30 RPM for 20 minutes. This duration was chosen because a preliminary test had shown that another 10 minutes only lowered the PO_2 by a further 1 or 2 mmHg. The syringes were submerged in water at 37°C. At 5-minute intervals the gas volumes were expelled and replaced with fresh gas mixture. The blood samples in the second set of five syringes were then oxygenated in the same manner as above with the oxygenating gas mixture.

After agitation a small volume from each syringe was injected into the Corning 178 pH/blood gas analyser (Ciba Corning Diagnostics Ltd, Halstead, UK) and drawn into capillary tubes for packed cell volume PCV) measurement by the microhaematocrit procedure (Hawksley Ltd, England). The remaining volume in each syringe was reduced to 1 ml for viscometry. Apparent whole blood viscosities were measured at 37°C with a Wells-Brookfield Cone-Plate rotational viscometer (model LVT, Stanford, CA) which was calibrated immediately prior to the study. Our viscosity assays were 'apparent' because they were only at one shear rate, whereas viscosity of a non-Newtonian fluid is theoretically the slope of the tangent of the curved plot of shear stress against shear rate. The viscometer was purged with the appropriate gas mixture to minimise gas exchange during the period of the assay. This was achieved by passing the gas through a nozzle attached to the barrel of the viscometer which did not interfere with any moving parts. It took 3½ hours to complete the above procedure for five subjects from venepuncture to the last viscosity measurement. The investigator who did all the studies was masked for the patients' retinopathy status.

Besides measuring whole blood viscosity we also report on the viscosity corrected for PCV variation by the methods described by Dormandy.[9] At venepuncture samples were also taken for HbA1 levels. All diabetic patients underwent regular biochemical screening. Plasma glucose (Beckman Glucose analyser), and HbA1 were measured at every visit. Total serum cholesterol and triglyceride levels, however, were assayed less frequently but, because of an association with retinopathy,[10 11] were recorded for those patients who had these tests on blood taken at the same time as that for viscometry.

To study the reproducibility of the relationship between the oxygenated and deoxygenated viscosities the viscosity measurements were repeated several weeks later on 11 normal persons. The results on each occasion were expressed as a ratio of the deoxygenated divided by the oxygenated viscosity, which was called the 'hypoxic viscosity ratio'. Reproducibility scores were calculated for each individual by expressing the difference between the two ratios (the signs being ignored) as a percentage of the mean and then subtracting this from 100. Correlation tests (least squares method) were carried out between viscosity values and ratios described above and independent variables – that is, HbA1, blood glucose, serum total cholesterol, serum triglycerides, and age. Student's *t* tests were used to compare groups of data, and p values less than 0·05 were considered significant.

Results

For the 11 normal persons the reproducibility

TABLE II *Results of viscometry of normal persons and diabetics. The shear rate was 230 s^{-1}, which is similar to that thought to prevail in the major retinal veins*

	Normal		*Diabetics without retinopathy*		*Diabetics with retinopathy*
Number	*23*	*p value**	*23*	*p value§*	*34*
Measured viscosities (cps)†					
Oxygenated viscosity	4·31 (0·53)	0·73	4·26 (0·40)	0·001	4·72 (0·56)
Deoxygenated viscosity	4·32 (0·47)	0·53	4·22 (0·55)	<0·001	4·84 (0·71)
Paired *t* test	0·89		0·53		0·041
Corrected viscosities (cps)‡					
Oxygenated viscosity	4·57 (0·39)	0·14	4·42 (0·30)	<0·001	4·82 (0·48)
Deoxygenated viscosity	4·54 (0·38)	0·31	4·42 (0·45)	0·001	4·95 (0·63)
Paired *t* test, p value	0·66		0·98		0·027
Hypoxic viscosity ratio	0·996 (0·065)	0·65	0·990 (0·017)	0·014	1·025 (0·064)

*Unpaired *t* tests between normal persons and diabetics without retinopathy. †Expressed as means (with standard deviations). ‡Corrected to standard PCV of 45% §Unpaired *t* tests between diabetics with and without retinopathy

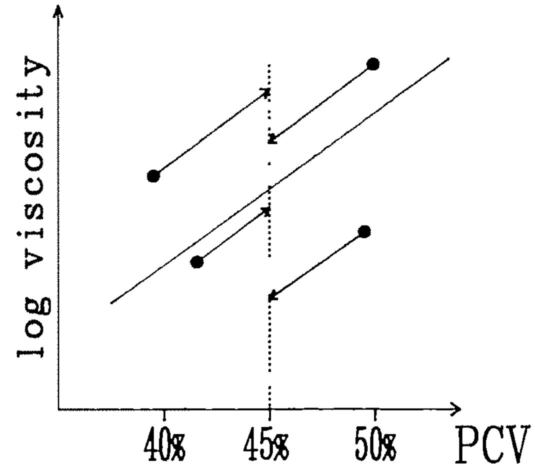


Figure 2: Correction of viscosity for variations of packed cell volume (PCV) for all subjects and patients. Data points (four sample ones are shown) were moved by computer to the 45% PCV line in a direction parallel to the linear regression line relating the log of the measured viscosity to the PCV for the group concerned.

scores ranged from 84·6 to 99·7 (mean 95·4). These scores are illustrated in Figure 1.

The viscosities of oxygenated and deoxygenated blood of normal persons and diabetics without and with retinopathy are presented in Table II. The PCV corrected viscosity is shown in Figure 2, where the slope of the linear regression line was calculated separately for each group concerned, at the same shear rate of 230 s^{-1}. The log of viscosity is used because of its greater correlation with PCV. The whole blood viscosity of normal persons and diabetics without retinopathy did not change significantly when deoxygenated (paired *t* tests, p=0·66 and 0·98 respectively for corrected values). In contrast the blood from patients with retinopathy became more viscous when deoxygenated (p=0·027). This pattern was seen with both the measured and corrected values.

Blood gas analyses on 56 samples (20 normals and 36 diabetics) showed that after oxygenation the mean values for PO_2 were 124·7 (SD 17·2) mmHg and for PCO_2 40·4 (1·6) mmHg. After deoxygenation the values for PO_2 were 18·3 (SD 2·8) mmHg and for PCO_2 were 54·1 (2·3) mmHg. The desired changes in blood gases were achieved with good reproducibility, indicated by the relatively small standard deviations.

The results of corrected viscosities of separate retinopathy groups together with the results of the other blood tests performed are presented in Table III. The biggest differences of viscosities are between the no-retinopathy group and the maculopathy and postphotocoagulation groups. In particular there were no significant differences between the HbA1 levels of the retinopathy groups. A scatterplot of the corrected deoxygenated viscosities is shown in Figure 3 to illustrate the spread of data.

Correlation studies showed a significant relationship between total serum cholesterol and the hypoxic viscosity ratio for the 29 patients who had these assays at the same time as the viscometry:

$$HVR=0\ 02\times C+0\ 89,\ r=0\ 44,\ p=0\ 018$$

where HVR is the hypoxic viscosity ratio and C is the total serum cholesterol level (mmol/l). The relationship was the same for corrected and measured viscosities and is illustrated in Figure 4. Cholesterol also correlated with deoxygenated viscosity (0·24×C+3·3, r=0·45, p=0·013) but not with oxygenated values. There were no other statistically significant correlations between any of the viscosity values and any of the other independent variables tested, namely, glucose, HbA1, triglycerides, and age. There was no correlation between cholesterol and either HbA1 or blood glucose.

The first 18 samples (6 normal and 12 diabetic) had PCVs measured of both oxygenated and deoxygenated portions. Of these, seven (three normal) showed a slight increase of PCV on deoxygenation (mean 2·6%) seven (three normal) showed a decrease (mean 2·5%), and four (one normal) showed no change. Only seven of the 18 pairs of PCVs reflected the change in viscosity. Owing to this lack of pattern all the following samples only had one estimate of PCV, performed on the original venous sample.

Discussion

The study was undertaken to test the hypothesis that blood from diabetic patients becomes more viscous when deoxygenated. The hypothesis has been supported in part: blood from diabetics with retinopathy was significantly more viscous when deoxygenated in contrast to that of normals and diabetics without retinopathy. However, this tendency (expressed as a 'hypoxic viscosity ratio') did not correlate with HbA1 but did with total serum cholesterol to a modest degree (r=0·44).

The correlation with cholesterol indicates that, of the factors influencing the hypoxic ratio, only 19% (r^2) can be attributed to the serum cholesterol level. Although cholesterol has been reported to affect membrane viscosity[12] and rigidity[13] and to correlate with the severity of

TABLE III *Results of viscometry and blood tests for 57 diabetic patients divided into retinopathy groups. The viscosities have been corrected to a PCV of 45%. The values are expressed as means (with standard deviations). The shear rate was 230 s^{-1}. The figures in parentheses, unless otherwise obvious, are p values (<0·05) for unpaired t tests with the no-retinopathy group*

	No retinopathy	*Background*	*Maculopathy*	*Postphotocoagulation*
Number	23	11	9	14
Oxygenated viscosity cps	4·42 (0·30)	4·47 (0·47)	4·86 (0·51) (0·005)	4 86 (0 50) (0·002)
Deoxygenated viscosity cps	4·42 (0·45)	4 77 (0·59)	5·00 (0 58) (0 005)	5 05 (0 70) (0·002)
Hypoxic viscosity ratio	0·990 (0 017)	1 007 (0·069)	1 028 (0 030) (<0 046)	1 037 (0 075)
PCV%*	42 7 (3·8)	43 4 (4·5)	42·7 (4 9)	43 9 (4·3)
HbA1%	7 7 (2·1)	7 7 (1·5)	7·6 (2 1)	8·0 (2·0)
Blood glucose mmol/l	9 2 (3 6)	14 2 (6 7)	10 2 (2·8)	9·6 (6 2)
Total serum cholesterol mmol/l	5 3 (1 4) (n=5)	5 6 (1 4) (n=8)	7 3 (1 8) (n=5)	6·5 (1·2) (n=11)
Serum triglycerides mmol/l	1·2 (0 6) (n=5)	2·3 (2·2) (n=8)	4·0 (4 8) (n=5)	1 7 (1·2) (n=11)

*Normal persons in this study: PCV 42·2 (3·7)%, HbA1 4·3 (0 6)% Normal ranges for the hospital blood glucose 3 5–5·0 mmol/l, total serum cholesterol 4 0–6 5 mmol/l, and triglycerides 0–2·0 mmol/l

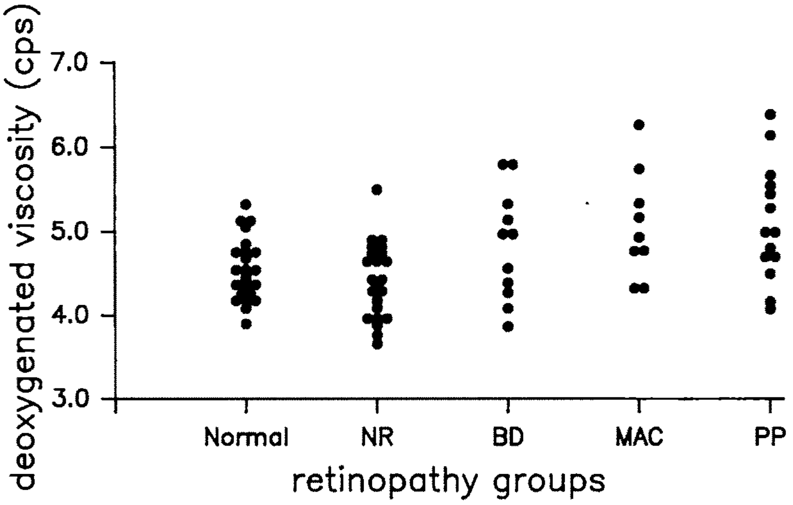


Figure 3: Deoxygenated viscosity of 23 normal persons and 57 diabetic patients measured at 230 s^{-1} and corrected to a PCV of 45%. NR=no retinopathy. BD=background retinopathy only. MAC=maculopathy. PP=postphotocoagulation. The deoxygenated viscosity of the patients in the maculopathy and postphotocoagulation groups were 13% ($p=0{\cdot}013$) and 14% ($p=0{\cdot}007$) higher than that of patients without retinopathy respectively.

diabetic retinopathy,[10] it is just as likely that the diabetic metabolic state itself is interfering directly with blood viscosity rather than through abnormal cholesterol levels. It was recently shown that red cell deformability was the same in diabetics with and without retinopathy (n=30, presumably under conditions of full oxygenation).[14] In the same study red cell membrane cholesterol content was lower in patients with retinopathy than those without ($p<0{\cdot}025$) in contrast to the plasma levels, which were the other way around ($p<0{\cdot}05$). In our study there was no relationship between cholesterol and HbA1 (or blood glucose), which might have been expected, since bad control is associated with increased levels of cholesterol.

The deoxygenating gas mixture was designed to bring the PO_2 down from the normal mixed venous level of about 40 mmHg to just below that of retinal venous blood, which is approximately 25 mmHg.[8] It is probable that the oxygen tension of blood in the deepest retinal capillaries will be lower still than that of mixed retinal venous blood. The PO_2 of the oxygenated samples is about 25 mmHg higher than true arterial blood, but the difference in saturation of the erythrocytes is of no consequence. The phenomenon of hypoxic viscosity may be a result of the combination of highly glycated haemoglobin and high cholesterol or other components of the blood. Haemoglobin is glycated at the terminal valine of the β chain – the same site of attachment of 2,3 diphosphoglycerate (DPG).[15] This substance, apart from facilitating the release of oxygen from haemoglobin, favourably affects the solubility of normal deoxygenated haemoglobin,[16] which may therefore be reduced if DPG is displaced by glycation. Fibrinogen is one blood component, for example, which has been reported to influence blood viscosity in diabetes[17] but was not measured in this study.

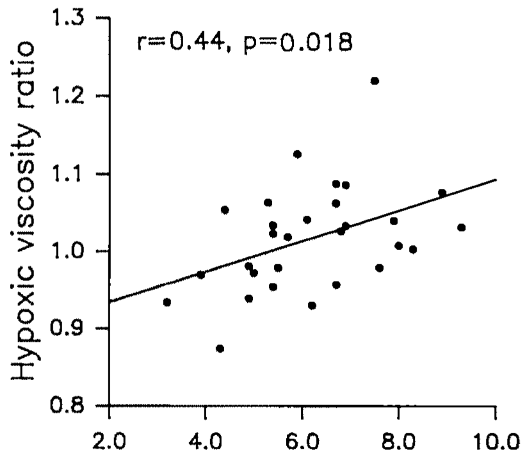


Figure 4: The hypoxic viscosity ratio (HVR) plotted against total serum cholesterol (C) for 29 diabetic patients. The HVR is the ratio of the deoxygenated divided by oxygenated viscosities, measured at the shear rate of 230 s^{-1} (similar to that in the major retinal veins). The regression line is represented by HVR=0·02×C+0·89.

Some increase in viscosity on deoxygenation may be expected in normal persons because the chloride shift is supposed to cause a 3% rise in PCV in venous blood.[18] This rise was not seen consistently in this study perhaps because the microhaematocrit method was not sensitive enough. The viscosity measurements in this study were carried out at the shear rate of 230 s^{-1} because this most closely resembles the shear rate thought to prevail in the retinal veins. The data of Riva *et al*[19] and Feke *et al*[20] show that the centre-line velocity of blood in a retinal vein of 180 μm diameter is 1·9 and 3·2 cm/s respectively, indicating average shear rates of 281 and 474 s^{-1}.* Red blood cells are subjected to changing shear rates during their passage through the vascular system. The plug flow in capillaries requires them to change shape rapidly in order to maximise contact between their cell membranes and the capillary endothelium. The shear rate in this situation is not well defined but is probably high.

Blood from the patients with retinopathy was 12% more viscous when deoxygenated than deoxygenated blood from diabetic patients without retinopathy ($p=0{\cdot}001$, Figure 3, Table III). This could mean reductions in blood flow, which may not be adequately corrected by autoregulation because the PO_2, PCO_2 and pressure of blood in the retinal arteries is normal. Previous studies on retinal vascular autoregulation have demonstrated vascular responses to abnormal changes in *arterial* blood including PO_2, PCO_2[21], systemic blood pressure,[22] blood glucose,[23 24] and pharmacological agents.[25 26] Initial demonstrations of an increase in blood flow in response to dark adaptation[27 28] were later questioned[29] and explained as an artifact of the laser doppler system.[30] There is no evidence that retinal blood flow can increase *in the absence* of changes in arterial blood parameters, but the vessels may be able to respond directly to tissue hypoxia.

To maintain volume blood flow in the face of increased viscosity there must be an increase in pressure gradient and/or dilatation of vessels (and hence a reduction in velocity). Venous dilatation and lower velocities are seen in practice in diabetic retinopathy.[31] Any increase in pressure gradient would cause a rise in capillary intraluminal and transmural pressure and predispose to oedema. In the event of volume blood flow not being fully corrected the consequence could be chronic mild hypoperfusion of the retinal tissue, which could lead to hypoxia and a rise in concentration of waste products of metabolism, such as toxic oxidative radicles, which are considered by some to be important in the development of diabetic complications.[32] In advanced retinopathy increased hypoxic viscosity could set up a vicious circle by leading to reduced blood flow and lower oxygen tensions, which would cause further increase in viscosity. However, the fact that it was only the patients with the most severe retinopathy who showed an increase in hypoxic viscosity suggests that this is the result of the same diabetic microenvironment which caused the retinopathy rather than the cause of the retinopathy itself; nevertheless the retinopathy could be worsened by it.

---

*Average shear rate=(−4/3)×(max velocity/radius) This is derived from an integration of the radially dependent shear rate over the cross sectional area, assuming Poiseuille flow since the Reynolds number is only 0 7.

The phenomenon of hypoxic viscosity could be important because it might present a new target for pharmacological attack. A future study will examine whether the deformability of red blood cells from diabetic patients is affected by oxygen tension.

The authors would like to express their appreciation to Victoria Rimmer, RGN, and Drs Robert Linsenmeier, Thomas Goldstuck and Paul Sullivan for helpful discussions, Professor Stephen Bloom for allowing his patients to be included in this study, Rod Braun MS for shear rate calculations, and Dr Emile Chen for invaluable help in preparing the manuscript.

This work was supported by the British Council for the Prevention of Blindness.

1 Department of Health and Social Security. Reports on Public Health and Medical Subjects No. 129. *Blindness and partial sight in England 1969–1976*. London: HMSO, 1979.
2 Weingeist TA. *Congressional testimony in support of the Citizens' Budget Proposal for the National Eye Institute for fiscal year 1990* New York· Research to Prevent Blindness, 1989
3 Condon PI, Serjeant GR Ocular findings in homozygous sickle cell anemia in Jamaica *Am J Ophthalmol* 1972; 73: 533–43
4 Goldberg MF Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol* 1971; 71: 649–65.
5 Anderson B, Saltzmann HA. Retinal oxygen utilization measured by hyperbaric blackout *Arch Ophthalmol* 1964; 72: 792–5
6 Alder VA, Cringle SJ, Constable IJ. The retinal oxygen profile in cats. *Invest Ophthalmol Vis Sci* 1983; 24: 30–6.
7 Linsenmeier RA Effects of light and darkness on oxygen distribution and consumption in the cat retina. *J Gen Physiol* 1986; 88: 521–42.
8 Sebag J, Delori FC, Feke GT, Weiter JJ Effects of optic atrophy on retinal blood flow and oxygen saturation in humans. *Arch Ophthalmol* 1989, 107: 222–6.
9 Dormandy JA Measurement of whole blood viscosity. In: Lowe GD, Barbenel JC, Forbes CD, ed *Clinical aspects of blood viscosity and cell deformability*. New York: Springer 1981 67–78
10 Dornan TL, Carter RD, Bron A, *et al* Low density lipoprotein cholesterol. an association with the severity of diabetic retinopathy. *Diabetologia* 1982; 22: 167–70
11 Mohan R, Mohan V, Susheela L, *et al* Increased LDL cholesterol in non-insulin dependent diabetics with maculopathy. *Acta Diabetol Lat* 1984; 21: 85–9
12 Feinstein MB, Fernandez SM, Sha'afi RI. Fluidity of natural membranes and phosphatidylserine and ganglioside dispersions. Effects of local anesthetics, cholesterol and protein. *Biochim Biophys Acta* 1975; 413: 354–70
13 Duax WL, Wawrzak Z, Griffin JF, Cheer C. Sterol conformation and molecular properties In. Yeagle PL. *Biology of Cholesterol*. Boca Raton CRC Press, 1988. 1–18
14 Zamorano AF, Arnalich F, Ferro-Sanchez A, Grande C, Laboz C, Pallardo LF Deformabilidad eritrocitaria y lipidos de la membrana eritrocitaria en la diabetes mellitus. *Med Clin (Barc)* 1987; 89: 717–20.
15 Bunn HF, Gabbay KH, Gallop PM The glycosylation of hemoglobin: relevance to diabetes mellitus. *Science* 1978, 200: 21–7.
16 Friederichs E, Lakomek M, Winkler H, Tillman W. Effects of calcium ions and 2,3 DPG on the solubility of deoxygenated human hemoglobin. *Clin Hemorheol* 1988; 8: 707–14.
17 Barnes AJ, Locke P, Saidde PR, *et al.* Is hyperviscosity a treatable component of diabetic microvascular disease? *Lancet* 1977; ii: 789–91
18 Ganong WF *Review of medical physiology* 6th ed Los Altos: Lange, 1973 487
19 Riva CE, Grunwald JE, Sinclair SH, Petrig BL. Blood velocity and volumetric flow rate in human retinal vessels. *Invest Ophthalmol Vis Sci* 1985, 26: 1124–32
20 Feke GT, Tagawa H, Deupree DM, *et al* Blood flow in the normal human retina. *Invest Ophthalmol Vis Sci* 1989; 30: 58–65
21 Hickam JB, Frayser R. Studies of the retinal circulation in man *Circulation* 1966, 33: 302–16
22 Robinson F, Riva CE, Grunwald JE, Petrig BL, Sinclair SH. Retinal blood flow autoregulation in response to an acute increase in blood pressure. *Invest Ophthalmol Vis Sci* 1986; 27: 722–6
23 Atherton A, Hill DW, Keen H, Young S, Edwards EJ The effect of acute hyperlycaemia on the retinal circulation of the normal cat *Diabetologia* 1980, 18: 223–7
24 Fallon TJ, Sleightholm MA, Merrick C, Chahal P, Kohner EM The effect of acute hyperglycaemia on flow velocity in the macular capillaries. *Invest Ophthalmol Vis Sci* 1987, 28: 1027–30.
25 ffytche TJ, Bulpitt CJ, Archer D, *et al.* Effects of papaverine on the retinal microcirculation. *Br J Ophthalmol* 1973; 57: 910–20.
26 Yan HY, Chiou GC. Effects of L-timolol D-timolol, haloperidol and domperidone on rabbit retinal blood flow measured with laser doppler method. *Ophthalmic Res* 1987; 19: 45–8.
27 Feke GT, Zuckerman R, Green GJ, Weiter JJ Response of human retinal blood flow to light and dark. *Invest Ophthalmol Vis Sci* 1983; 24: 136–41
28 Riva CE, Grunwald JE, Petrig BL. Reactivity of the human retinal circulation to darkness· a laser doppler velicometry study *Invest Ophthalmol Vis Sci* 1983; 24: 737–40.
29 Hill DW, Houseman J. Retinal blood flow in the cat following periods of light and darkness. *Exp Eye Res* 1985; 41: 219–25.
30 Riva CE, Petrig BL, Grunwald JE. Near infrared retinal laser doppler velicometry. *Laser Ophthalmol* 1987; 1: 211–5.
31 Grunwald JE, Riva CE, Sinclair SH, *et al* Laser doppler velocimetry study of retinal circulation in diabetes mellitus. *Arch Ophthalmol* 1986; 104: 991–6.
32 Wolff SP. The potential role of oxidative stress in diabetes and its complications novel implications for theory and therapy In: Crabbe MJC, ed. *Diabetic complications, scientific and clinical aspects*. Edinburgh· Churchill Livingstone, 1987 167–220.

For those patients who should avoid taking nonselective ocular beta blockers...

> “Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”[1]

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

A bright outlook for glaucoma patients

For effective control of IOP
minimising the risks associated with
nonselective beta-blockade [2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only β_1 selective ocular beta blocker

SELECTIVE β_1 BETA BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have been reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depressive neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies have not demonstrated any specific hazard there are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response this drug should be used during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known whether Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is administered to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed from the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml droptainer. **PRODUCT LICENCE HOLDER AND NUMBER:** Alcon Laboratories U.K 0649/0097

DATE OF PREPARATION JANUARY 1990

Further information is available on request

Alcon

SPECIALISTS IN EYE CARE

Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

REFERENCES:

1. Jones FL, Ekberg NL. Letter N Eng J Med 1979; **301**: 270
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62
3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184

British Journal of Ophthalmology, 1990, 74, 405–408

A single dose of the topical carbonic anhydrase inhibitor MK-927 decreases IOP in patients

N Pfeiffer, R Hennekes, E A Lippa, F Grehn, H Garus, F L Brunner-Ferber

Abstract

MK-927 is a novel topical carbonic anhydrase inhibitor (CAI). We present the first single-dose clinical trial of MK-927 in 24 patients with bilateral primary open-angle glaucoma or ocular hypertension. This investigation was conducted as a two-centre, double-masked, randomised, placebo controlled study. Patients received one drop of 2% MK-927 in one eye and placebo in the other eye. Modified diurnal intraocular pressure (IOP) curves were performed before the study and on one treatment day. A single dose of 2% MK-927 induced a peak mean IOP decrease of 10·5 mmHg at 4·5 hours postdose. With compensation for diurnal variation, as determined by the prestudy diurnal pressure curve, the net peak mean reduction of IOP caused by MK-927 was 7·5 mmHg versus a corresponding net change of 1·4 mmHg in the contralateral placebo treated eye. Thus a single dose of MK-927 gave a clinically significant IOP reduction in patients.

At present, the medical treatment of glaucoma depends mainly on the topical application of parasympathomimetics, sympathomimetics, and β-blockers. Oral CAIs have been in use for the treament of glaucoma since 1954.[1] Despite their efficacy, lack of ocular side effects and little escape phenomenon their clinical use is limited because of systemic side effects. These include paraesthesiae, fatigue, gastrointestinal disturbances, and loss of libido, all resulting in poor patient compliance. In addition serious side effects such as renal calculi, electrolyte imbalance, and aplastic anaemia may also occur. From 1955 onwards[2,3] attempts have been made to use acetazolamide in a topical preparation which it was hoped would have the advantages of an oral CAI while avoiding its systemic side effects. However, intraocular penetration was insufficient to produce a substantial reduction of IOP. Various other CAIs applied topically have been disappointing clinically despite encouraging results in pharmacological models.[4] Recently a new gel formulation of aminozolamide (6-amino-2-benzothiazole sulphonamide) has been shown to reduce the IOP to some extent when applied topically.[5] Another agent, 6-hydroxybenzo[b]-thiophene-2-sulphonamide, reduced the IOP in rabbits[6] but failed to do so in man.[7]

The compound MK-927 (5, 6-dihydro-4-(2-methylpropyl) amino-4-H-thieno-(2, 3-b) thiopyran-2-sulphonamide 7, 7-dioxide hydrochloride, see Fig 1 for structural formula) is a new, highly water soluble CAI.[8,9] When given topically it reduces the IOP in normotensive rabbits[10] in the α-chymotrypsin rabbit model of ocular hypertension[11] and in laser induced ocular hypertensive cynomolgus monkeys.[12] Topical 2% MK-927 was shown to be acceptably tolerable and to reduce the IOP in healthy, normal volunteers.[13]

We now report the first single-drop study of MK-927 in patients with primary open-angle glaucoma or ocular hypertension.

Patients and methods

The study was reviewed and approved by the Ethical Review Committee of Freiburg University. Informed consent was obtained from each patient before entering the study.

Patients were selected from two German University Eye Hospitals based on a medical history and an ophthalmological examination consistent with the diagnosis of primary open-angle glaucoma or ocular hypertension. Patients were to be male or postmenopausal or sterilised females. Exclusion criteria were: history of angle closure or secondary glaucoma, history of intraocular surgery or ocular trauma; ocular inflammation; concomitant medication affecting IOP; visual acuity worse than 20/100; wearing of contact lenses; or significant risk from discontinuation of the current glaucoma medication.

If patients were considered eligible all previous hypotensive therapy was discontinued for a minimum of 72 hours for parasympathomimetics and 14 days for all other ocular hypotensive medications. After that washout period the patients returned to the clinic, and a prestudy diurnal IOP curve was performed with IOPs measured bilaterally at 1000, 1100, 1200, 1300, 1430, 1600, and 1800 hours. To be admitted into the study, the IOP at 1000 had to be ≥24 mmHg in each eye, with a difference between eyes of ≤6 mmHg.

MK-927

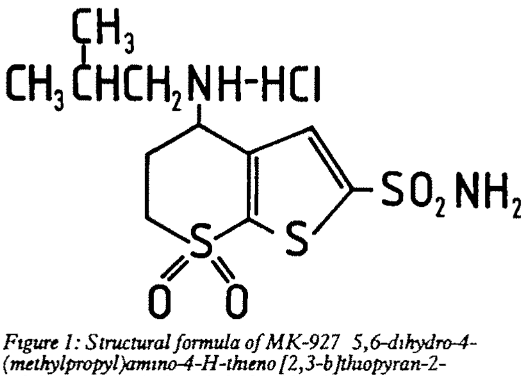


Figure 1: Structural formula of MK-927 5,6-dihydro-4-(methylpropyl)amino-4-H-thieno [2,3-b]thiopyran-2-sulphonamide 7,7-dioxide hydrochloride

Universitäts-Augenklinik Freiburg, West Germany
N Pfeiffer
F Grehn
Universitäts-Augenklinik Berlin, West Germany
R Hennekes
H Garus
Merck Sharp and Dohme Research Laboratories, West Point, USA
E A Lippa
F L Brunner-Ferber

Correspondence to:
Dr Norbert Pfeiffer
Universitäts-Augenklinik
Freiburg, Killianstr. 5, D-7800 Freiburg, West Germany.

Accepted for publication 2 February 1990

TABLE I *Schedule of observations*

	Prestudy day, day −14 to −2	Treatment day — Time after administration of drug: 0*	0†	10 min	30 min	1 h	2 h	3 h	4·5 h	6 h	8 h
Pretreatment diurnal IOP curve (day −7 to −2)	X‡										
Symptomatology	X	X		X	X	X	X	X	X	X	X
Visual acuity	X	X		X	X	X	X	X	X	X	X
Anterior segment examination	X	X		X	X	X	X	X	X	X	X
Intraocular pressure	X†	X				X	X	X	X	X	X
Instillation of MK-927/placebo			X								
Ophthalmoscopy	X										X§
Gonioscopy (within 6 months)	X										
Visual field (within 3 weeks)	X										

*Immediately predose.
†To be at 1000.
‡Intraocular pressures taken at 1000, 1100, 1200, 1300, 1430, 1600, 1800.
§To be done as final examination of the day

The patients returned two to seven days after the prestudy diurnal curve had been done. Visual acuity was tested, and bilateral IOPs were measured at 1000. Immediately afterwards one eye received one drop of 2% MK-927 ophthalmic solution and the other eye received one drop of placebo (vehicle). This was followed by a diurnal IOP curve like that before the study, namely, at 1, 2, 3, 4·5, 5, 6, and 8 hours after treatment. At 10 and 30 minutes after treatment and before all measurements of IOP, the visual acuity was tested, an examination of the anterior segment was performed, and the patients were asked about symptoms (Table I).

This investigation was conducted as a two-centre, double-masked, randomised, placebo-controlled study. The administration of MK-927 or placebo to the right or left eye was randomised.

STATISTICAL METHODS

Differences between prestudy day and treatment day diurnal curves were compared at each time point by a paired *t* test (2-tailed, type I error set at 0·05). The primary response variable way was change in IOP from predose on the treatment day minus the corresponding IOP change on the prestudy diurnal curve. A between-eye analysis was done by analysis of variance.

Results

Twenty-seven patients entered the study, but two had to be excluded for inadvertent concomitant ocular hypotensive treatment and one for previous exposure to atropine. Hence 24 patients completed the study in accordance with the protocol, 8 males and 16 females (age 36 to 82 years, mean 65 years). Nineteen patients had primary open-angle glaucoma, five had ocular hypertension. Prior to the washout period, nine had received β-adrenoceptor blocking agents alone, seven pilocarpine alone, three pilocarpine plus an adrenergic agonist, one guanethidine plus an adrenergic agonist, and one acetazolamide alone. Three patients had no prior ocular hypotensive therapy.

TABLE II *Effect of a single drop of 2% MK-927 versus placebo*

	MK-927 treated eye			Placebo-treated eye		
Time	Prestudy day	Treatment day	p*	Prestudy day	Treatment day	p*
1000	30·5 (1·2)	30·9 (1·5)	ns	30·6 (1·3)	30·4 (1·4)	ns
1100	30·3 (1·4)	26·3 (1·4)	0·05	30·2 (1·5)	28·6 (1·5)	0·05
1200	29·1 (1·3)	22·9 (1·3)	0·001	28·7 (1·4)	27·7 (1·5)	ns
1300	27·8 (1·1)	21·1 (1·1)	0·001	27·4 (1·3)	26·7 (1·5)	ns
1430	27·5 (1·2)	20·4 (0·9)	0·001	26·7 (1·3)	25·3 (1·3)	ns
1600	26·5 (1·3)	21·3 (0·9)	0·01	26·4 (1·3)	25·5 (1·3)	ns
1800	26·9 (1·3)	23·6 (1·3)	0·05	27·1 (1·3)	26·9 (1·7)	ns

Mean IOP (SEM) in mmHg of 24 patients on prestudy and treatment day.
*p Indicates significance values for differences between prestudy and treatment day determined by paired *t* test NS=not significant (p>0·05)

At 1000 on the prestudy diurnal curve day the IOP ranged from 24 to 45 mmHg, the mean being 30·5 mmHg for the eyes to be treated with MK-927 and 30·6 mmHg for the eyes to be treated with placebo (Table II). The mean differences between eyes did not exceed 0·8 mmHg at any time point. As expected, diurnal variation occurred, with the IOP being lower in the afternoon (Fig 2).

On the treatment day the eyes treated with MK-927 showed a sustained decrease of IOP throughout the diurnal curve, with a peak mean change from predose pressure of −10·5 mmHg (peak mean percentage change −33·1%) at 4·5 hours after treatment (Table III). At eight hours after treatment the mean IOP of MK treated eyes had not returned to prestudy day levels. In contrast, placebo treated eyes showed a peak mean change of −5·1 mmHg (−16·6%) at 4·5 hours. At 8 hours the mean IOP had returned to prestudy day levels (Fig 2). When comparing prestudy and treatment-day diurnal curves we noted a significant difference in the mean IOP of the MK-927 treated eyes at all time points after treatment (Table II). In contrast, for the contralateral eyes we noted a significant difference between IOP on prestudy and treatment day only at 1 hour after treatment. The mean decrease in IOP in MK-927 treated eyes on the treatment day was significantly greater than the mean decrease on the prestudy day at each point after treatment, p<0·01 (Table III).

To compensate for diurnal variation in the IOP we calculated the net change in IOP (ΔΔ-IOP) at each time point on the treatment day. For each time point this was defined as the change in IOP from immediately before treatment (1000) on the treatment day minus the corresponding change in IOP from 1000 on the prestudy diurnal curve day. MK-927 treated eyes showed a peak mean ΔΔ-IOP of −7·5 mmHg at 4·5 hours after treatment, while the

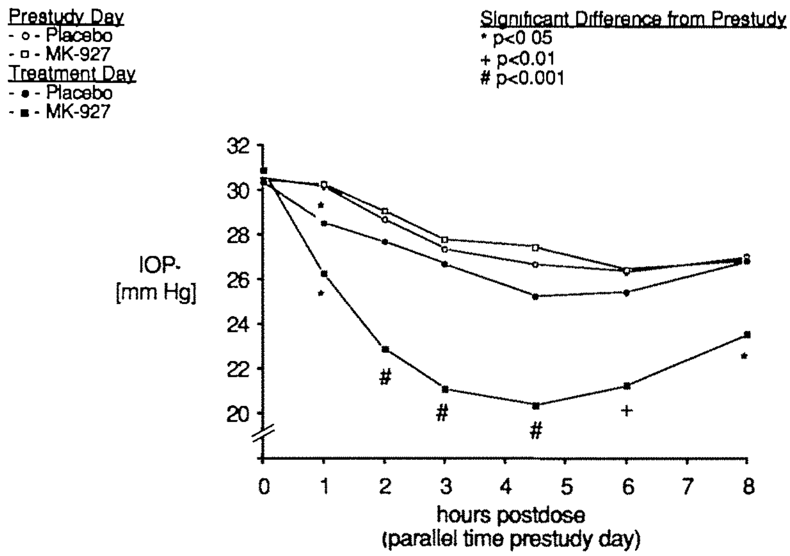


Figure 2: Mean IOP. Diurnal curves on prestudy day (○) and treatment day (●). Level of significance between MK-927 and placebo treated eyes at the same time (paired t test); n=24 for each point.

peak mean ΔΔ-IOP for placebo treated eyes was −1·4 mmHg and occurred at 1 hour after treatment (Fig 3). At each time point the mean ΔΔ-IOP was significantly greater for MK-927 treated eyes than for placebo treated eyes (p<0·01).

Pressure reduction was not analysed according to iris colour since the distribution was uneven (17 blue, three hazel, two green, two brown).

The patients were monitored for local side effects. Four patients reported bilateral blurring of vision and one patient bilateral foreign body sensation at 10 minutes after treatment. One patient had burning at 10 min in the MK-927 treated eye. Visual acuity remained unchanged in most patients and dropped one to three lines in five MK-927 treated eyes and in six placebo treated eyes, usually at 10 min after treatment. Mild bilateral corneal punctate erosions were seen towards the end of the day in 16 patients and were considered to be induced by repeated applanation tonometry. One patient had bilateral conjunctival hyperaemia. No systemic side effects were observed.

Discussion

MK-927 is a topical CAI which has been shown to have IOP lowering activity after single doses in several animal models and after three doses in man. In this study we show that in patients with primary open angle glaucoma or ocular hypertension a single drop of 2% MK-927 induced a sustained decrease in IOP over at least eight hours. A net peak mean reduction in IOP of 7·5 mmHg above that due to diurnal variation alone occurred at 4·5 hours after treatment (Fig 3). This result is similar to that obtained in a multiple dose study in which three consecutive doses of 2% MK-927 elicited a peak mean IOP decrease of 7·7 mmHg (26·9%).[14]

TABLE III *Mean change and percentage change (with SEM) from predose on treatment day*

	MK-927 treated eyes		*Placebo treated eyes*	
Time	*Change**	*% Change*	*Change*	*% Change*
1100	−4·6 (0·7)	−14·7%	−1·8 (0·4)	−6·0%
1200	−8·0 (0·9)	−25·6%	−2·7 (0·7)	−9·2%
1300	−9·8 (0·9)	−31 4%	−3 7 (0·6)	−12·4%
1430	−10·5 (0·9)	−33·1%	−5 1 (0 5)	−16·6%
1600	−9·6 (1·0)	−29·9%	−4·8 (0·4)	−16·0%
1800	−7·3 (0·6)	−23 6%	−3 5 (0 8)	−12 5%

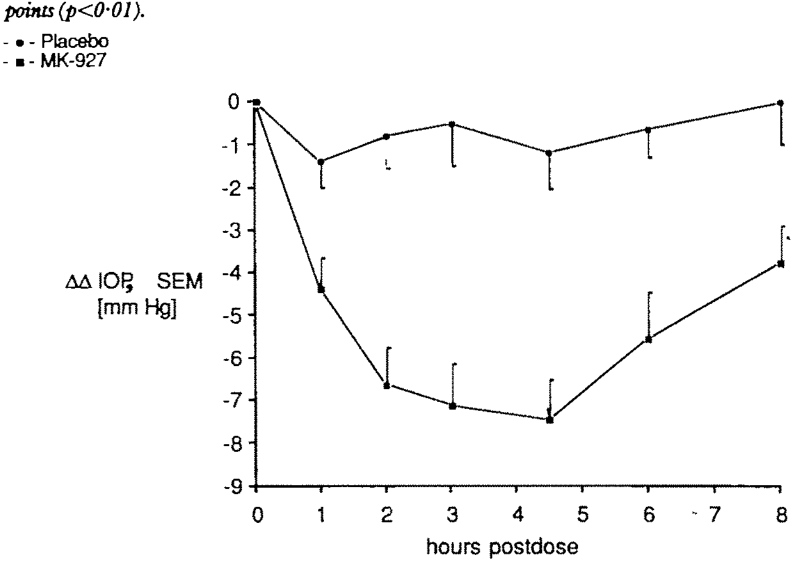
*IOP changes for MK-927 treated eyes are significantly different from those for placebo treated eyes at all time points (p<0·01).

A slight reduction of IOP in the contralateral placebo treated eyes might be deduced from Figure 2. However, this is significant at only one time point and is probably due to day-to-day changes in diurnal variation. Moreover, the amount of drug available for systemic absorption is so small that a contralateral effect based on a systemic effect is unlikely.

The patients did not complain of symptoms apart from transient blurring of vision and in one case of a transient burning sensation in an MK-927 treated eye. This suggests good toleration of the drug. However, as the IOPs were measured immediately before application of the drug, in most cases the cornea was still anaesthetised when the drops were instilled, obviously limiting subjective symptoms.

The high level of activity which the drug shows after the application of a single drop is quite promising. It is expected that a topical CAI might avoid side effects common to systemic CAIs while retaining the advantage of substantial activity and little escape phenomena. If this proves to be true and the pressure reduction demonstrated here persists with chronic use of the drug, MK-927 might be suitable for the treatment of glaucoma or ocular hypertension. It is also likely that therapy with a topical CAI could be combined with that of other pressure lowering medications.

Figure 3: Mean net change in IOP (ΔΔ-IOP) determined by: Fall of IOP from t=0 hour on treatment day minus fall of IOP from t=0 hour on pretreatment day with standard error of the mean. ΔΔ-IOP for MK-927 treated eyes is significantly different from placebo treated eyes at all time points (p<0·01).



STATEMENT ON POSSIBLE PROPRIETARY OR COMMERCIAL INTEREST

Dr Lippa is a director, clinical research, and Dr Brunner-Ferber is an assistant director, clinical pharmacology, both are employed at Merck & Co , Inc

Drs Pfeiffer, Grehn, Hennekes, and Garus have no commercial or proprietary interest in the drug MK-927

We acknowledge the contributions of Ms Coleen Clineschmidt, senior medical program co-ordinator, clinical research, Merck Sharp and Dohme Research Laboratories, for assistance in co-ordinating the various aspects of this study, and of Ms Karen Walton, Ms Deborah Panebianco, and Ms Rayanne Berman, statisticians, biostatistics, Merck Sharp and Dohme Research Laboratories, for performing the statistical analysis of the study data

1 Becker B Decrease in IOP in man by a CAI, Diamox *Am J Ophthalmol* 1954; 37: 13–5

2 Foss RH Local application of Diamox, an experimental study of its effect on the intraocular pressure. *Am J Ophthalmol* 1955; 39: 336–9

3 Nagasubramanian S, Bloom J, Poinoosawmy D, *et al. The effects of a topical acetazolamide preparation on IOP in patients with ocular hypertension. In· Krieglstein. GK ed. Glaucoma Update III* Heidelberg Springer, 1987 225–9.

4 Maren TH Carbonic anhydrase general perspectives and advances in glaucoma research. *Drug Dev Res* 1987; 10: 255–76

5 Lewis RA, Schoenwald RD, Barfknecht CF, *et al* Aminozolamide Gel. a trial of a topical CAI in ocular hypertension. *Arch Ophthalmol* 1986, 104: 842–4

6 Maren TH, Bar-Ilan A Effect of 6-OH benzo[b]thiopene-2-sulfonamide, a new topical carbonic anhydrase (CA) inhibitor on IOP in rabbits *Invest Ophthalmol Vis Sci* 1987; 28 (suppl) 268

7 Werner EB, Gerber DS, Yolande JY Effect of a topical CAI, 6-OH benzo[b]thiopene-2-sulfonamide, on IOP in normotensive subjects *Can J Ophthalmol* 1987; 22: 316–9

8 Ponticello GS, Freedman MB, Habecker C, *et al.* Thienothiopyran-2-sulfonamides a novel class of water-soluble CAI. *J Med Chem* 1987; 30: 591–7.

9 Baldwin J, Ponticello G, Sugrue M, *et al* MK-927, a water soluble, topically effective CAI Read at the Third Chemical Congress of North America, Toronto, Canada, 5 June, 1988

10 Maren TH, Bar-Ilan A Ocular pharmacology and hypotensive activity of a topically active carbonic anhydrase (CA) inhibitor, a 4-alkylaminothienothiopyran-2-sulfonamide, MK-927 *Invest Ophthalmol Vis Sci* 1988; 29 (suppl): 16.

11 Sugrue MF, Gautheron P, Grove J, *et al* MK-927 a topically effective ocular hypotensive carbonic anhydrase (CA) inhibitor in rabbits. *Invest Ophthalmol Vis Sci* 1988; 29 (suppl): 81

12 Wang RF, Serle JB, Podos SM, *et al.* The ocular hypotensive effect of the topical carbonic anhydrase (CA) inhibitor MK-927 in glaucomatous monkeys. *Invest Ophthalmol Vis Sci* 1988, 29 (suppl): 16.

13 Lippa EA, von Denffer HA, Hofmann HM, *et al.* Local tolerance and activity of MK-927, a novel CAI. *Arch Ophthalmol* 1988; 106: 1694–6

14 Lippa E, Hofmann H, Feicht B, *et al.* MK-927: a topically effective CAI in patients. Read at the Third Congress of the European Glaucoma Society at Estoril, 1988.

Effects of topical timolol (0·5%) and betaxolol (0·5%) on corneal sensitivity

S S Weissman, P A Asbell

Abstract

There are conflicting reports on the propensity of topical β blockers to produce corneal anaesthesia. We measured corneal sensitivity thresholds quantitatively for 10 minutes following the administration of one drop of topical timolol maleate (0·5%), betaxolol hydrochloride (0·5%), or saline in 30 eyes of 18 normal subjects in a randomised, double-masked study. Most subjects had insignificant changes in corneal sensitivity thresholds. We identified, however, a subgroup of four subjects (five eyes) that had a marked and prolonged increase of corneal sensitivity threshold (corneal anaesthesia) after timolol (three eyes) and betaxolol (two eyes). The group mean age of these 'responders' (49·0 years) was significantly greater ($p<0·005$) than that of the non-responders (35·0). We recommend periodic measurements of corneal sensitivity in older patients receiving topical timolol or betaxolol, especially when given in higher concentrations, to identify responders, who may be at risk of developing keratitis.

β Blockers are first line drugs for topical therapy of primary open-angle glaucoma. They lower the intraocular pressure mainly by depressing the production of aqueous. Local anaesthetic effects of β blockers may be from membrane stabilisation[1 2] or inhibition of corneal epithelial chloride transport,[3] which is independent of their β blocking effect.

Timolol maleate, the first topical β blocker available in the United States, is a non-selective β_1 and β_2-adrenergic antagonist. Van Buskirk[4] reported corneal anaesthesia in four of 25 patients taking topical timolol and in a separate study[5] observed that, of 547 reports of adverse ocular reactions to topical timolol, 20 mentioned superficial punctate keratitis, with coexistent corneal anaesthesia in eight. More recent studies have conflicted in regard to the incidence and severity of corneal anaesthesia produced by topical timolol.[6-11]

Betaxolol hydrochloride, a newer, selective β_1 adrenergic antagonist has been observed by some authors to cause mild, transient corneal anaesthesia after topical use,[6 12 13] while this was not observed by others.[9-11 14-16] We conducted a randomised, double-masked, clinical trial measuring the quantitative corneal anaesthetic side effects of the use of one drop of topical timolol 0·5% and betaxolol 0·5%.

Materials and methods

We studied 30 eyes of 18 normal subjects. We excluded subjects who had previous ocular surgery, photocoagulation, trauma, corneal inflammation, or infection; those who had used topical or systemic medicines known to alter corneal sensitivity, pregnant women, contact lens wearers, diabetics, and patients older than 60. (Persons above 60 years of age[8] may have decreased corneal sensitivity.)

Twenty-five subjects were enrolled in this study. Five were excluded because of excessive eye movement and/or inconsistent measurements during baseline threshold testing. Two other patients failed to keep scheduled appointments.

We dynamically measured corneal sensitivity thresholds using the electronic optical aesthesiometer developed by Draeger. During measurement the stimulus body length remains constant and in contact with the cornea, while the exerted force is expotentially increased by the investigator, which permits all measurements to be completed within the physiological blink interval. When subjects perceive a touch sensation, they depress a button that automatically terminates stimulus body contact with the cornea, and the threshold force (between 0 and 999×10^{-5} newtons) is displayed on a digital LED indicator. All threshold measurements were performed by one investigator (SSW).

Ten subjects received one drug (timolol, betaxolol, or saline), four subjects received two drugs, and four subjects received three drugs during the course of the study, in a randomised, double masked fashion. (Three subjects complained of stinging after betaxolol administration, thereby unmasking the drop to the investigator) In the multiple drug group a two-week washout period followed drug administrations. A subject never received the same drug more than once during the study.

The timolol group consisted of 10 subjects, eight females and two males, with a mean age of 41·2 (range 27–53) (Table I). Seven were black; three were white. The betaxolol group consisted of nine subjects, six females and three males, with a mean age of 35·9 (range 27–55) (Table I). Five were black, four were white. The saline control group consisted of 11 subjects, 10 females and one male, with a mean age of 39·1 (range 29–49) (Table I). Eight were black, three were white.

The baseline threshold was determined 1 mm central to the 6 o'clock limbal position (the average of three successive measurements performed 30 seconds apart). Measurements at the corneal centre would have been less useful, as small anaesthetic side effects might have been missed at this area of maximal sensitivity. Following drug administration of one drop in the conjunctival cul-de-sac, and gentle eyelid closure

Department of Ophthalmology, Mount Sinai School of Medicine, New York, USA
S S Weissman
P A Asbell

Correspondence to:
Scott S Weissman, MD,
Manhattan Eye, Ear and Throat Hospital,
Department of Ophthalmology, 210 East 64th Street, New York,
NY 10021, USA.

Accepted for publication
18 January 1990

TABLE I *Relative change in corneal sensitivity thresholds*

		Number of minutes after drug instillation									
		1	2	3	4	5	6	7	8	9	10
Timolol (n=10)	Mean relative change from baseline (SD)*	14·9 (35·9)	29·5 (72·9)	46·0 (123·0)	43·4 (105·1)	35·9 (87·4)	16·6 (18·5)	29·4 (75·0)	14·1 (21·0)	10·9 (20·5)	26·2 (70·9)
Betaxolol (n=9)	Mean relative change from baseline (SD)	12·3 (36·7)	16·3 (37·1)	14·2 (36·2)	14·3 (36·1)	14·7 (35·9)	10·8 (20·1)	9·8 (19·7)	5·6 (12·3)	14·4 (36·1)	15·2 (36·1)
Saline (n=11)	Mean relative change from baseline (SD)	16·2 (53·0)	18·2 (52·3)	10·8 (20·5)	2·7 (4·3)	12·1 (33·3)	14·9 (33·5)	14·4 (34·6)	9·9 (26·9)	3·3 (7·6)	1·8 (3·2)

* We obtained an unsatisfactory threshold measurement at one of the 10 measurement periods after drug instillation in three patients This threshold was assumed to be the average of the preceding and subsequent measurement Paired *t* testing comparing thresholds at time x and time x+1 minutes within drug groups confirmed the validity of this assumption.
Relative change from baseline at time x minutes =

$$\frac{\text{threshold at time x minutes} - \text{threshold at baseline}}{\text{threshold at baseline}}.$$

for 5 seconds, corneal sensitivity thresholds were remeasured at the same position at 1-minute intervals for 10 minutes.

The measurements were continued for 20 minutes if thresholds had not returned to baseline at 10 minutes. The subjects were required to blink between measurements to prevent corneal desiccation.

STATISTICAL ANALYSIS

At each measurement period (minutes 1 to 10 after drug instillation) we compared the mean relative change in corneal sensitivity thresholds* in the timolol and betaxolol groups to a saline control group using *t* tests. We analysed intragroup changes in relative corneal sensitivity thresholds by F ratio tests. We compared mean ages of responders and non-responders in the timolol and betaxolol groups by *t* tests. We considered $p \leq 0·05$ to be significant.

Results

There was no significant change in relative corneal sensitivity thresholds in any of the drug groups (p=0·015), and at no time interval (1 to 10 minutes) after drug instillation was there any significant difference in mean relative changes in thresholds among the three drug groups. However, three eyes tested with timolol and two eyes tested with betaxolol showed marked corneal anaesthesia, which persisted for longer than 10 minutes in all cases.

In the saline group relative changes in thresholds were mild and transient.*

Responders (subjects who had at least a fivefold relative increase in corneal sensitivity threshold which persisted for at least 5 minutes) had the threshold of their untreated contralateral eye measured at 10 minutes. This was done to ensure that corneal anaesthetic effects produced in the treated eye were produced by the drug and were not due to patient fatigue or other non-drug-related factors. All responders had thresholds in the untreated eye that were not significantly different from baseline thresholds in the treated eye, lending support to observer reliability.

One responder received all three drops during the course of the study (Fig 1). After timolol administration her relative change in thresholds included 8·9 at 1 minute and a peak of 26·8 at 13 minutes. A marked corneal anaesthetic effect (relative change in threshold of 16·4) persisted at 20 minutes. After receiving betaxolol this subject had the following relative change in thresholds: 110.0 at 1 and 10 minutes and 25·6 at 20 minutes. After saline administration this subject had relative threshold changes of 4·7 at 5 minutes and 9·0 at 6 minutes, but the remainder of the measured thresholds were approximately equal to baseline.

A second responder received both timolol and saline during the course of the study. Relative threshold changes after timolol were 231·5 at 2 minutes, 394·5 at 3 minutes, and 9·0 at 20 minutes. After saline testing, relative changes in thresholds were 5·1 at 4 minutes, 15·8 at 6 minutes, and 1·3 at 10 minutes. The third responder received timolol only and had relative threshold changes of 16·6 at 4 minutes, a peak of 21·7 at 5 minutes, and a return to baseline at 19 minutes. The fourth responder received only betaxolol and had relative threshold changes which peaked at 13·5 at 3 minutes, with a return to baseline by 19 minutes.

The responders (timolol and betaxolol groups combined) ranged in age from 39 to 53 with a mean age of 49·0 (SD 6·2). The non-responders differed significantly, they ranged in age from 27 to 52 and had a mean age of 35·0 (SD 8·8) (<0·005).

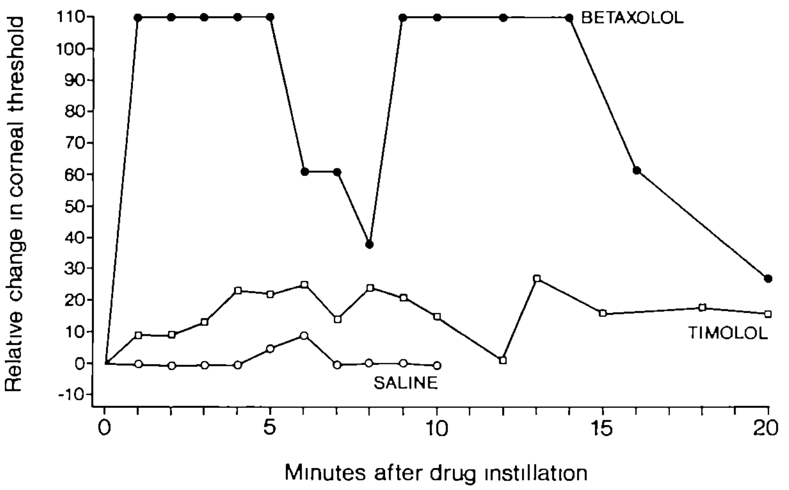


Figure 1: Note the marked and prolonged corneal anaesthesia in this subject after timolol, and after betaxolol administration.

---

*Relative change from baseline at time x minutes=

$$\frac{\text{threshold at time x minutes} - \text{threshold at baseline}}{\text{threshold at baseline}}.$$

*Differing baseline values obtained from the same subject on different days, and variability in threshold values following saline administrations, were presumed to be due to the inexact placing of the stimulus body on the cornea, and variation in subject response times

Discussion

The cornea has a rich sensory nerve supply, which is derived from the ophthalmic division of the trigeminal nerve. Trigeminal neurons are presumed to transport trophic substances which regulate the corneal epithelial respiratory, glycolytic, and mitotic activity. Postulated mediators of this tropic effect include epinephrine,[17–20] cyclic AMP,[3] acetylcholine,[17] serotonin,[21] and substance P.[22] The clinical effects of these metabolic derangements associated with corneal anaesthesia include epithelial defects, stromal ulceration, and perforation.

The mechanism of β blocker induced corneal anaesthesia has not been delineated. The demonstration of adrenergic corneal nerves in variety of species,[17 18] as well as the increased corneal epithelial chloride transport[3] and decreased mitotic rate[19 20] following β adrenergic stimulation, suggest an adrenergic regulation of the corneal epithelium. In addition topical timolol has been reported to antagonise dopamine stimulated release of norepinephrine from sympathetic nerve endings in isolated rabbit corneal epithelium.[23] However, the local anaesthetic properties of β blockers are probably independent of β blockade.[24]

Stabilisation of ocular axonal cell membranes has also been proposed as the mechanism for the local anaesthetic actions of β blockers.[12] However, Yasuhara and associates[25] demonstrated a dissociation between membrane stabilisation and corneal anaesthetic side effects in rats after topical β blocker administration.

An alternative mechanism is the antagonism by β blockers of serotoninergic activation of corneal epithelial chloride transport.[21 26] A variety of β blockers have been shown to have a strong affinity for the 5 HT binding site.[27] The importance of serotoninergic nerves in corneal sensation is suggested by the detection of serotonin in bovine corneal nerves[28] and human aqueous humour,[29] and also by the increase in both corneal epithelial acetylcholine content and corneal sensitivity in rabbits following serotonin administration.[30]

Vale and associates[31] as early as 1972 described corneal anaesthesia with topical propanolol use. Van Buskirk[4 5] reported both severe· corneal anaesthesia and superficial punctate keratitis resulting from topical timolol use. All of Van Buskirk's patients with markedly diminished corneal sensation were more than 70 years of age.

More recent reports[6–16 32] have conflicted with regard to the incidence and severity of corneal anaesthetic side effects produced by topical timolol and betaxolol. A variety of methods were used in these studies to measure corneal sensitivity (Table II). Draeger[8] used the aesthesiometer employed in the present study and found transient corneal anaesthetic effects following a one-time administration of topical timolol, but only in subjects older than 40. He also noted subjects in whom marked and prolonged corneal anaesthetic effect occurred following administration of several different β blockers. He postulated a genetically determined enzyme variation to explain these patients' susceptibility to β blocker induced corneal anaesthesia.

We did not detect in 18 subjects (30 eyes) significant relative change in corneal sensitivity thresholds from baseline in either the timolol or the betaxolol groups in comparison with placebo (saline) group. We compared relative changes in thresholds at each measurement interval (1-10 minutes after drug administration) between the three drug groups, and found no point at which a significant intergroup difference existed.

We identified a subgroup of four subjects (five eyes) that showed marked and prolonged corneal anaesthetic effects after topical timolol (three eyes) and topical betaxolol (two eyes). One

TABLE II *Timolol and betaxolol studies*

Study	*Drugs tested*	*No of patients*	*Mean age (yr)*	*Method of measuring corneal sensitivity*	*Duration of study*	*No of patients with corneal anaesthesia*
Van Buskirk[4]	Timolol (?%)	547 adverse reactions	?	?	?	8 (20 had superficial punctate keratitis)
Van Buskirk[5]	Timolol (0·5%)	25	? (range (45–84)	Cotton wisp	13 weeks	4 with marked anaesthetic effect, all in patients older than 70
Spinelli *et al*[7]	Timolol (0·25% & (0·5%)	30	57	Cotton wisp and Cochet Bonnet aesthesiometers	18 months	3 with remarkably decreased sensitivities
Draeger[8]	Timolol (0·25%, 0·5% 1%)	20	? (range 20–60)	Draeger aesthesiometer	15 minutes	Rapid and transient anaesthetic effects, only in patients older than 40
Allen *et al*[9]	Timolol (0·25% and 0·5%) and Betaxolol (0·25% & 0·5%)	38	65	Cochet Bonnet aesthesiometer	26 weeks	5, all noted in patients who had received timolol
Hoh[11]	Timolol (0·5%) and Betaxolol (0·5%)	40	31	Draeger and Cochet Bonnet aesthesiometers	30 minutes	Marked and prolonged anaesthesia noted in 1 patient after betaxolol
Present study	Timolol (0·5%) & Betaxolol (0·5%)	18 (30 eyes)	40	Draeger aesthesiometer	20 minutes	Marked and prolonged anaesthesia noted in 4 patients; in 2 after timolol, in 1 after betaxolol, and in 1 after both timolol and betaxolol
Radius[12]	Betaxolol (0·125%)	20	?	Cotton wisp	6 weeks	Several patients with mild anaesthetic effects before, during, and after treatment interval, but no difference between betaxolol and placebo
Berrospi and Leibowitz[14]	Betaxolol (0·25%)	12	67	Cotton wisp	52 weeks	0 (but transient superficial keratitis in several)

responder had a corneal anesthetic effect which persisted for 20 minutes on two occasions, once after receiving timolol and again after receiving betaxolol. The magnitude of the absolute increase in thresholds was similar in this subject after receiving both timolol and betaxolol, but the relative increase in thresholds was greater after betaxolol owing to higher baseline thresholds measured prior to timolol administration.

The two other responders who received timolol (but not betaxolol) had a return of their corneal thresholds to baseline at 10 minutes and 19 minutes respectively. The responder who received betaxolol (but not timolol), had a return of thresholds to baseline at 19 minutes.

The mean age of responders to timolol or betaxolol was significantly greater than that of non-responders ($p<0{\cdot}005$). The youngest responder was 39 years of age.

The indentification in this study of a subgroup of generally older patients showing marked and prolonged corneal anaesthetic side effects after topical timolol 0·5% confirmed previous investigations by Van Buskirk,[4] Spinelli and associates,[7] and Draeger.[8] In addition, we demonstrated that this effect may also occur after topical betaxolol 0·5% administration.

The failure of many previous reports to document these corneal anaesthetic side effects of topical timolol and betaxolol may be attributed in some instances to use of lower concentrations of topical β blockers, use of less sensitive methods to measure corneal sensitivity, and to study populations which consisted of mostly young subjects with few or no responders.

We recommend performing periodic corneal aesthesiometry in patients receiving topical timolol and betaxolol to identify responders. More frequent monitoring is suggested in patients with pre-existing corneal hypoaesthesia, in older patients, and in those receiving higher concentrations of these topical β blockers. If a significant keratitis is shown to occur frequently in responders treated with topical β blockers, therapy with an alternative class of intraocular pressure lowering medication may be preferable in these susceptible patients.

This study was supported in part by grant NEI EY 01867

1 Jaillon P, Heckle J, Weissenburger J, Cheymol G. Comparative dromotropic activity of timolol and propanolol in anaesthetized dogs. *Eur J Pharmacol* 1978; **47**: 129–34

2 Morales-Aguilara A, Williams EMV. The effects on cardiac muscle of beta-receptor antagonists in relation to their activity as local anaesthetics *Br J Pharmacol* 1965; **24**: 332–9

3 Chalfie M, Neufeld AH, Zadunaisky JA Action of epinephrine and other cyclic AMP-mediated agents on the chloride transport of the frog cornea *Invest Ophthalmol Vis Sci* 1972; **11**: 644–50

4 Van Buskirk EM Corneal anesthesia after timolol maleate therapy. *Am J Ophthalmol* 1979; **88**: 739–44.

5 Van Buskirk EM. Adverse reactions from timolol administration *Ophthalmology* 1980; **87**: 447–50.

6 Berry DP, Van Buskirk EM, Shields MB Betaxolol and timolol. a comparison of efficacy and side effects. *Arch Ophthalmol* 1984, **102**: 42–5

7 Spinelli D, Vigasio F, Montanari P Short-term and long-term timolol maleate effects on corneal sensitivity *Doc Ophthalmol* 1984; **56**: 385–92.

8 Draeger J. Local anesthetic effects of beta-blockers In: Draeger J, Ackermann M, Buhr-Unger H, *et al*, eds *Corneal sensitivity measurement and clinical importance.* New York. Springer, 1984 78–84.

9 Allen RC, Hertzmark E, Walker AM, Epstein DL A double-masked comparison of betaxolol vs timolol in the treatment of open-angle glaucoma. *Am J Ophthalmol* 1986, **101**: 535–·41.

10 Stewart RH, Kimbrough RL, Ward RL Betaxolol vs timolol a six month double-blind comparison *Arch Ophthalmol* 1986; **104**: 46–8

11 Hoh H Hornhautsensibilitat nach Einzeldosen von Timolol, Betaxolol oder Placebo bei Augengesunden-randomisierte, prospektive Doppelblindstudie. *Fortschr Ophthalmol* 1988; **85**; 132–8

12 Radius RL. Use of betaxolol in the reduction of elevated intraocular pressure *Arch Ophthalmol* 1983; **101**: 898–900

13 Weinreb RN, Rich R, Kushner FM Effect of adding betaxolol to dipivefrin therapy *Am J Ophthalmol* 1986; **101**: 196–8

14 Berrospi AR, Leibowitz HM Betaxolol, a new β-adrenergic blocking agent for treatment of glaucoma *Arch Ophthalmol* 1982; **100**: 943–6

15 Caldwell DR, Salisbury CR, Guzek JP Effects of topical betaxolol in ocular hypertensive patients *Arch Ophthalmol* 1984; **102**: 539–40

16 Feghali JG, Kaufman PL Decreased intraocular pressure in the hypertensive human eye with betaxolol, a β_1-adrenergic antagonist *Am J Ophthalmol* 1985; **100**: 777–82

17 Laties A, Jacobowitz D. Histochemical study of the adrenergic and the cholinergic innervation of the anterior segment of the rabbit eye. *Invest Ophthalmol Vis Sci* 1964, **3**: 592–600.

18 Tervo T, Palkama A Adrenergic innervation of the rat corneal epithelium *Invest Ophthalmol Vis Sci* 1976; **15**: 147–50

19 Friedenwald JS, Buschke W. The effects of excitement of epinephrine and of sympathectomy on the mitotic activity of the corneal epithelium in rats *Am J Physiol* 1944, **141**: 689–94

20 Mishima S The effects of the denervation and the stimulation of the sympathetic and the trigeminal nerve on the mitotic rate of the corneal epithelium in the rabbit *Jpn J Ophthalmol* 1957; **1**: 65–73

21 Martin XY, Safran AB. Corneal hypoesthesia. *Surv Ophthalmol* 1988, **33**: 28–40.

22 Tervo K, Tervo T, Eranko L, Vannas A, Cuello AC, Eranko O Substance P-immunoreactive nerves in the human cornea and iris *Invest Ophthalmol Vis Sci* 1982, **23**: 671–4

23 Crosson CE, Beuerman W, Klyce SD. Dopamine modulation of active ion transport in rabbit corneal epithelium. *Invest Ophthalmol Vis Sci* 1984, **25**: 1240–5

24 Fitzgerald JD Perspectives in adrenergic beta-receptor blockade *Clin Pharmacol Ther* 1969; **10**: 292–306

25 Yasuhara H, Sakamoto K, Ueda I, Dissociation between local anesthetic and membrane-stabilizing action in anti-arrhythmic beta-adrenergic blockers and local anesthetics. *Anesth Analg* 1981; **60**: 887–90

26 Klyce SD, Palkama KA, Harkonen AM, *et al* Neural serotonin stimulates chloride transport in the rabbit corneal epithelium *Invest Ophthalmol Vis Sci* 1982; **23**: 181–92.

27 Middlemiss DN, Blakeborough L, Leather SR. Direct evidence for an interaction of β-adrenergic blockers with the 5-HT receptor. *Nature* 1977; **267**: 289–90.

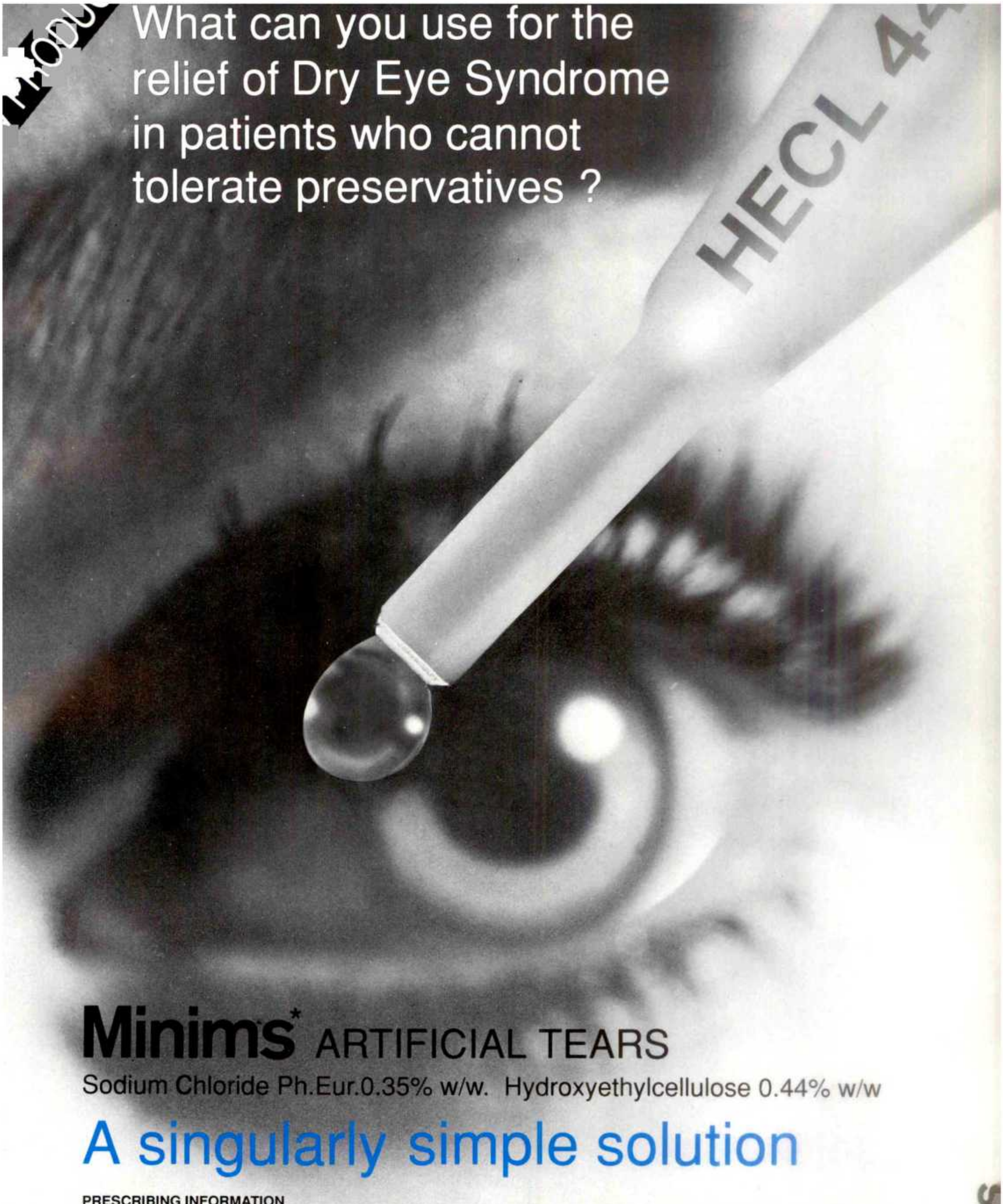
28 Osborne NN The occurrence of serotoninergic nerves in the bovine cornea *Neurosci Lett* 1983, **35**: 15–8.

29 Martin X, Brennan C, Lichter PR Serotonin in human aqueous humor. *Ophthalmology* 1988; **95**: 1221–6

30 Von Oer S Ueber die Beziehung des Acetylcholine des Hornhautepithels zur Erregungsubertragung von diesem auf die sensiblen Nervenden *Pflugers Arch* 1961, **273**: 325–34

31 Vale J, Gibbs ACC, Phillips CI Topical propanolol and ocular tension in the human eye *Br J Ophthalmol* 1972, **56**: 770–5

32 Calissendorf B Corneal anesthesia after topical treatment with timolol maleate. *Acta Ophthalmol (Kbh)* 1981; **59**: 347–9


What can you use for the relief of Dry Eye Syndrome in patients who cannot tolerate preservatives ?
HECL 4

Minims* ARTIFICIAL TEARS

Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

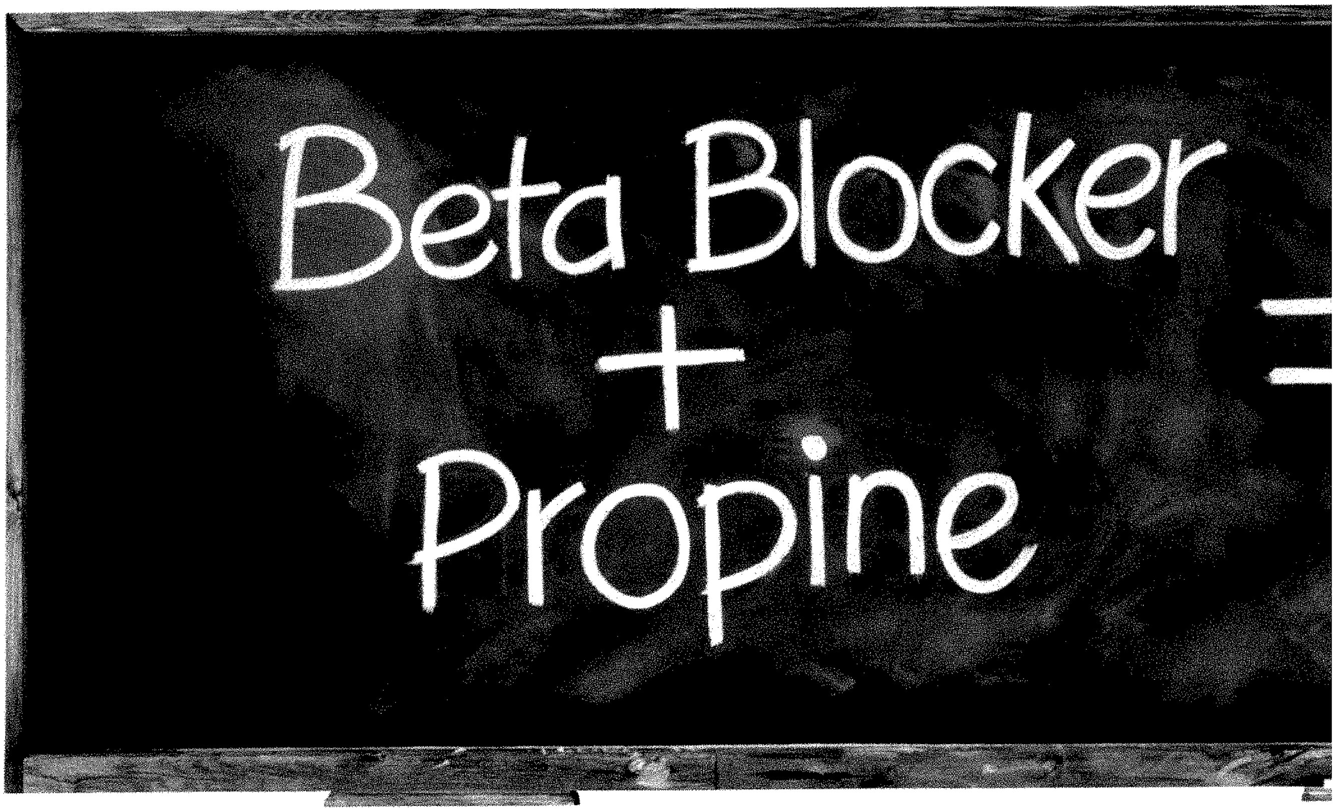
A singularly simple solution

PRESCRIBING INFORMATION
● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml.
Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

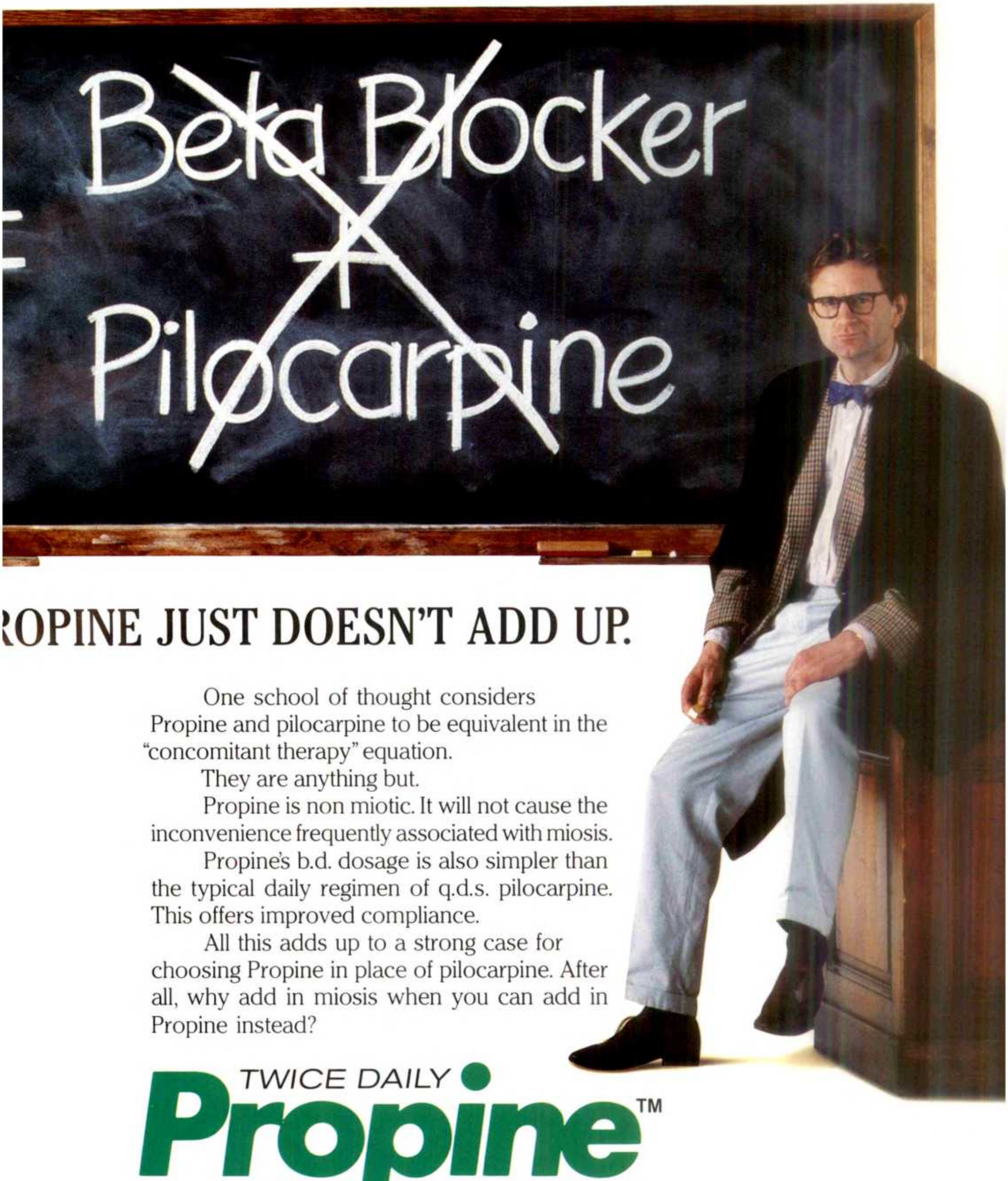
* Trade Mark

Smith+Nephew



EQUATING PILOCARPINE WIT

PROPINE™ Prescribing Information
Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be us
with caution in patients with narrow angles since dilation of the pupil may trigger
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrenal
use in aphakic patients. Prompt reversal generally follows discontinuance of the dr
Macular oedema with dipivefrin does present as a possibility in the aphakic patient. T
product contains benzalkonium chloride and should not be used by patients continu
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachycar
arrhythmias and hypertension have been reported with ocular administration



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY

Propine™

dipivefrin hydrochloride

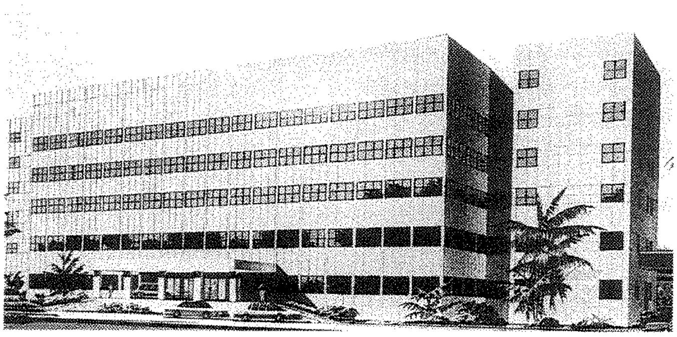
A CLEAR CHOICE IN THE GLAUCOMA EQUATION

naline, and may occur rarely with Propine therapy. Ocular: the most frequently
rted side-effects are conjunctival injection, and burning and stinging on instillation.
ound vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis,
been reported occasionally. Adrenochrome deposits in the conjunctiva and cornea
been associated rarely with use of dipivefrin. Follicular conjunctivitis has been
rted during long term therapy with Propine. The condition is reversible upon discon-
ance of the drug. **Pharmaceutical precautions** Store at room temperature. Discard
unused contents 28 days after opening the bottle. **Legal category** POM. **Package quantities** Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990

TM denotes trademark

ALLERGAN PHARMACEUTICALS

Singapore National Eye Centre



The Singapore National Eye Centre has been recently established to provide high quality patient care and to promote research and education for the prevention, diagnosis, and treatment of eye diseases. The 6000 square metres (65000 square feet) Centre has more than 25 consultation suites, 6 day-surgery operating theatres, a day recovery ward, a laser centre, research laboratories, a lecture theatre and patient education centre.

The Centre will be operational by October 1990.

The Singapore National Eye Centre welcomes applications for:

Ophthalmic Positions

...at all levels.

Ophthalmologists, Research Fellows,
Orthoptists, Optometrists,
Ophthalmic Nurses and Technicians

◆ Excellent career opportunities and attractive remuneration and benefits will be offered to the successful applicants.

Interested applicants please apply with full details to:

Dr Arthur S.M. Lim,
Medical Director
SINGAPORE NATIONAL EYE CENTRE
c/o Dept of Ophthalmology, National
University Hospital, Lower Kent Ridge
Road, Singapore 0511
Republic of Singapore

For rapid communication, please fax correspondence to **(65) 7796755.**

Applications requiring total confidentiality should indicate clearly "strictly confidential" on all correspondence and may be sent by fax to the personal fax number of ***Dr Arthur S.M. Lim at (65) 7333360.***

British Journal of Ophthalmology, 1990, 74, 413–416

Comparison of the effect of acetazolamide tablets and Sustets on diurnal intraocular pressure in patients with chronic simple glaucoma

P W Joyce, K B Mills

Abstract

Twenty patients with primary open-angle glaucoma uncontrolled on single topical therapy completed a double dummy crossover study to compare acetazolamide tablets with a sustained release formulation (Sustet). The two preparations were equally effective, but no direct relationship was found between the intraocular pressure and the plasma concentration of acetazolamide. No difference between the formulations was found in the frequency or severity of side effects.

Acetazolamide (Diamox) is a carbonic anhydrase inhibitor used in ophthalmology to control intraocular pressure (IOP).[1] It is prescribed in conjunction with single or multiple topical treatment, and has been available for many years in the UK as a 250 mg tablet. In the early 1960s a sustained release formation (Sustet) was marketed containing 500 mg of the active drug. Several studies have confirmed the efficacy of both preparations in lowering IOP.[2-8] However, many side effects have been encountered and were thought to be dose related with both formulations.[9 10] In an effort to reduce these effects smaller doses of acetazolamide have been tried over short periods of time.[11 12] However, no study has compared the effects of the same doses of the two formulations available in the UK on IOP over 12- or 24-hour dosage intervals.

Material and methods

As part of a study[13] of the role of acetazolamide in glaucoma 35 patients with primary open-angle glaucoma were enrolled in a double dummy crossover study to compare a once or twice daily dose of acetazolamide tablets with the same dose of Sustet. The IOP of these patients was inadequately controlled on single topical treatment (pilocarpine/timolol). All patients fulfilled the following criteria: IOP >22 mmHg, an open angle on gonioscopy, a glaucomatous field defect, and cupped optic discs. The exclusion criteria were previous intraocular surgery, ocular injury, ocular inflammation, and other types of glaucoma.

After giving written, informed consent each patient underwent a full physical and ocular examination. The latter included visual acuity (Snellen), visual fields (Goldmann), applanation tonometry, gonioscopy, and ophthalmoscopy. A blood sample was taken for a full blood count, liver function studies, and electrolyte analysis. Because previous studies[4 10] had indicated that patient tolerance was better on Sustet, each patient was started on a run-in dose of 500 mg of Sustet at 10 00 in addition to their topical therapy and was seen at weekly intervals between 09 00 and 10 00 in the outpatient department for one to two weeks. If the IOP was not controlled (22 mmHg or less) the dose was increased to a maximum of 500 mg twice daily (10 00 and 22 00). With control of the IOP each patient was maintained on this dose throughout the study Those patients not controlled were withdrawn and started on alternative treatment.

The patients whose IOP was controlled were allocated randomly to either acetazolamide tablets and dummy Sustet or dummy tablets and active Sustet. Each patient was seen weekly, when the IOP was checked and a blood sample taken for plasma acetazolamide estimation by high performance liquid chromatography (HPLC). After four weeks of treatment the patients were admitted for a 24-hour profile of their IOP. The times of the readings were at 08 00, 09 00, 10 00, 11 00, 12 00, 14 00, 16 00, 18 00, 22 00, 04 00, and 08 00. Blood was taken simultaneously for plasma acetazolamide estimation. At the end of the study each patient completed a questionnaire about specific side effects during the previous month's treatment. Before discharge each patient was given the alternative systemic formulation and seen again at weekly intervals in the outpatient department for four weeks. They were then readmitted for a second 24-hour profile. On this occasion in addition to their comments on the possible side effects each patient was asked if they had a preference for either period of treatment. Finally the patients completed a third profile of their IOP one week later after cessation of systemic treatment.

Results

Twenty patients completed the protocol. Of the 35 that were started on the run-in dose of Sustet 11 were withdrawn on account of side effects during this period. The remainder of the patients who were withdrawn did so during the crossover study – two on account of lack of control of IOP, one for personal reasons, and the other because of tinnitus exacerbated by an upper respiratory tract infection. Seventeen patients completed the third inpatient profile of their IOP while not taking acetazolamide. Three could not do so for personal reasons.

Of those patients who completed the crossover study 11 were on topical timolol 0·25% twice daily and the remaining nine were on pilocarpine 2% or 4% four times daily. Sixteen were taking 500 mg acetazolamide at night, one was on 500

Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH
P W Joyce
K B Mills

Correspondence to
Mr P W Joyce

Accepted for publication
18 January 1990

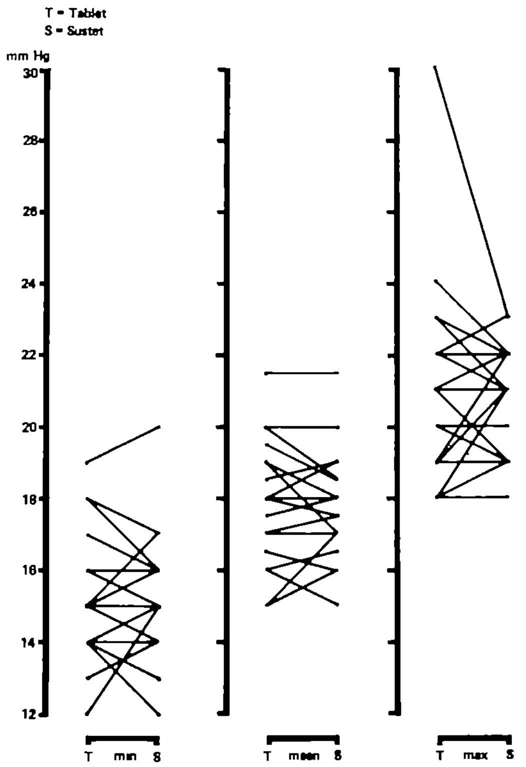


Figure 1: A comparison of the maximum, mean, and minimum IOP (mmHg) in the worse eyes of 20 patients who had been on acetazolamide tablets and Sustets.

mg in the morning, and three patients were taking 500 mg twice daily. Of the seventeen patients who completed the post withdrawal profile (control) 10 were on timolol and the remainder on pilocarpine.

The results of the 24-hour profiles of IOP in the worse eyes of those patients who completed the protocol showed that the mean, minimum, and maximum IOP were indistinguishable between both formulations (Fig 1). Furthermore the diurnal curves for the mean IOP were also similar (Fig 2). Nonetheless it is apparent from the post-withdrawal profile that acetazolamide did have an effect, as there was a considerable rise in IOP. Interestingly the difference between the mean IOP of those patients on timolol alone (25·31 mmHg, SD 0·7) and those on pilocarpine (25·42 mmHg, SD 1·43) was not significant (Fig 3).

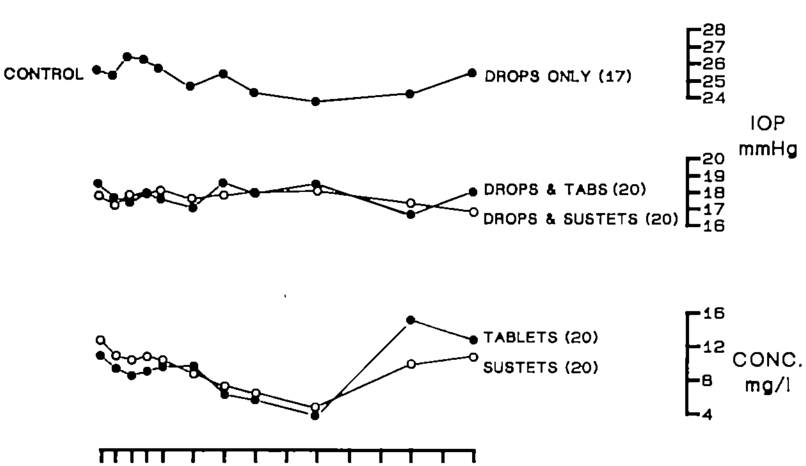


Figure 2: The mean diurnal profile on and off treatment with acetazolamide. The upper half of the profile refers to the IOP (mmHg) both on and off (control) systemic treatment. The lower half refers to the concentration of acetazolamide (mg/l) measured over the same period (tablets and Sustets).

It was noteworthy that there was little difference between the mean, minimum, and maximum plasma concentrations of both formulations (Fig 4) during the inpatient profiles. This could have been due to the fact that most patients had an evening dose and the peak concentration was therefore missed. Nevertheless the range on acetazolamide tablets (15·5 mg/l, SD 4·7) was greater than on Sustets (11·6 mg/l, SD 4·9). It was significant that there was no discernible relationship between the diurnal plasma concentration of acetazolamide (tablets or Sustets) and the IOP (Figs 2, 3). This is clearly demonstrated by the fact that there was no relationship between the mean plasma concentration and the highest IOP in the worse eyes (Fig 5).

The results of the questionnaire on specified side effects and their severity are presented in Table I. The number of patients reporting particular side effects on both formulations did not differ greatly. Furthermore there was no change in the blood counts of any patient. There was, however, a small reduction in the serum potassium during the first month but this was not sustained. The serum creatinine and bilirubin rose slightly during the same period but this tendency was not maintained for the remainder of the study.

At the end of the crossover study each patient was asked if he or she had a preference for either course of treatment. Of the 17 patients on once daily treatment one preferred the tablets, another the Sustets, and the rest had no preference. Of the three patients on twice daily treatment two preferred the Sustet, one found it easier to swallow, and the second felt better. The third patient had no preference.

Discussion

Recent studies on acetazolamide have concentrated on the short term effects on IOP.[11][12] In particular Friedland *et al*[11] showed that a dose of 63 mg of acetazolamide produced a drop of IOP which higher doses did not increase significantly in a group of ocular hypertensives. This dose gave a plasma value of 4–5 mg/l, which is calculated to give 99% inhibition of carbonic anhydrase in the ciliary epithelium. In our study the mean plasma concentration on acetazolamide tablets was 8·6 mg/l (SD 2·8) and on Sustets was 9·7 mg/l (SD 3·8). This could account for the satisfactory control of IOP in this group of patients, but the topical treatment may have had an overriding influence. However, the withdrawal of acetazolamide produced a significant rise in IOP (Fig 2). Perhaps a future study might look at the plasma levels in those patients whose IOP was not controlled satisfactorily on a given regimen.

Berson *et al*[14] showed that there was no significant difference in the ability of 500 mg Sustet given twice daily to lower the IOP in comparison with 250 mg of acetazolamide tablet four times a day in a group of glaucomatous patients uncontrolled on one or more topical

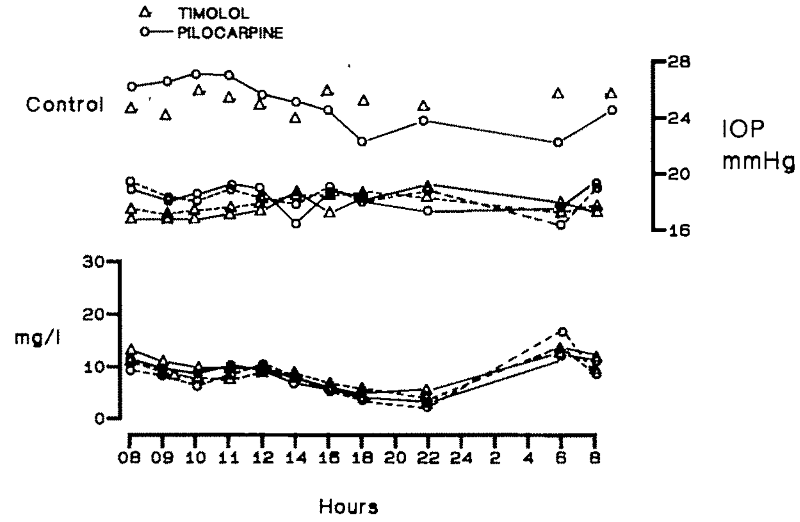


Figure 3: The diurnal profiles for the patients on timolol (Δ) and pilocarpine (O). The upper half refers to the mean IOP (mmHg) on and off (control) acetazolamide in each group. The lower half refers to the mean concentration of acetazolamide (mg/l) measured over the same period (tablets or Sustets)

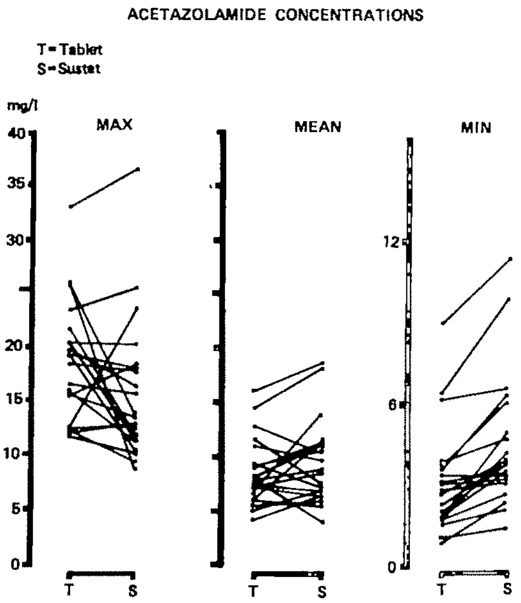


Figure 4 A comparison of the maximum, mean, and minimum acetazolamide concentration (mg/l) in the 20 patients who had been on tablets and Sustets.

agents. However, this was another short term study. In our study the mean IOP off acetazolamide was 25·1 mmHg (SD 1·4). It is interesting to observe that the mean IOP on both preparations was similar – 18 mmHg (SD 1·8) for tablets and 18·1 mmHg (SD 1·6) for Sustets. Since the majority of patients were on an evening dose of acetazolamide only, once daily treatment would appear to be adequate to control IOP. Furthermore the mean plasma level on acetazolamide tablets and Sustets was well above the suggested ideal plasma level of 5 mg/l.[15] This suggests perhaps that an even smaller dose of acetazolamide tablets (250 mg) should be tried initially for long-term treatment, whereas a higher dose (500 mg) has been shown to produce the highest reduction in IOP in the short term.[16] From the post-withdrawal profile (control, Fig 3) there is a trend for the diurnal curve on timolol to be smoother than on pilocarpine, confirming similar findings of McClure and Vogel[17] and Hass and Drance.[18]

TABLE I *Number of patients reporting side effects from acetazolamide on the cross-over study with the degree of severity on both formulations*

	Tablet			*Sustet*		
	Mild	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
Malaise	3			3		
Nausea	1			2		
Weakness	3			3		
Depression	1			0		
Paraesthesiae	10	8	1	12	7	
Alteration of taste	2			1		
Diarrhoea	3			4		
Anorexia	4			4		
Drowsiness	6			7		
Diuresis (short)	4			4		
Constipation	2			0		

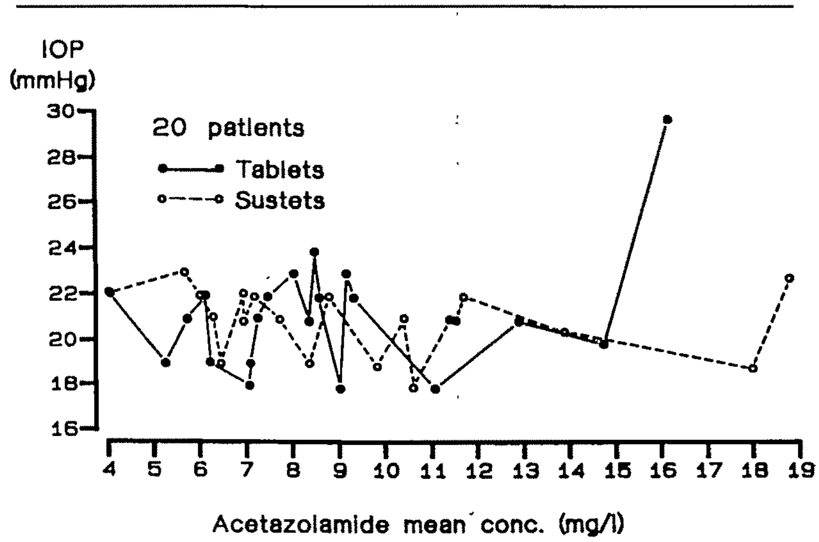


Figure 5. The mean concentration (mg/l) of acetazolamide in 20 patients versus the maximum recorded IOP (mmHg) in the worse eyes

During the run-in period of this study patients were started on 500 mg of Sustet in the morning to counteract the diurnal rise in IOP. However, 11 patients were withdrawn owing to side effects. In an attempt to improve recruitment an evening dose was tried. This reduced the incidence and severity of the side effects considerably. When the code of the trial was broken, it was surprising to find there was no significant difference in the number of patients reporting specified side effects on the two formulations of acetazolamide. This finding lends support for an evening dose schedule and perhaps to the common belief that the subjective side effects relate to the peak concentration, especially with long-term use.

In conclusion, most patients in this study, who had primary open-angle glaucoma uncontrolled on single topical treatment, were adequately controlled on the addition of 500 mg (2×250 mg) of acetazolamide tablets or one Sustet (500 mg) at night. The severity of side effects was also reduced. Thus an evening dose of acetazolamide in conjunction with topical therapy may well have a beneficial effect on compliance in the treatment of open-angle glaucoma.

1 Becker B Decrease in intraocular pressure in man by carbonic anhydrase inhibitor, Diamox *Am J Ophthalmol* 1954; 37. 13
2 Drance SM, Carr F Effect of sustained-release Diamox on the intraocular pressure in man *Br J Ophthalmol* 1961, 45 695–8
3 Mestre C, Galin M, McLean J Evaluation of sustained-release acetazolamide *Br J Ophthalmol* 1963, 47: 31–5
4 Garner L, Franklin CE, Ferweda J Advantages of sustained-release therapy with acetazolamide in glaucoma *Am J Ophthalmol* 1963; 55· 323–7

5 Becker B. Longterm acetazolamide (Diamox) administration in therapy of glaucomas *Arch Ophthalmol* 1955, 54: 187–92

6 Kupfer K, Lawrence C, Linner E Longterm administration of acetazolamide (Diamox) in the treatment of glaucoma. *Am J Ophthalmol* 1955; 40: 673–80

7 de Carvalho CA, Lawrence C, Stone H Acetazolamide (Diamox) therapy in chronic glaucoma *Arch Ophthalmol* 1958; 59: 840–9.

8 Garrison L, Roth A, Rundle H, Christensen R. A clinical comparison of three carbonic anhydrase inhibitors *Trans Pacific Coast Oto-ophthalmol Soc* 1967, 48: 137–45

9 Lichter P, Newman L, Wheeler N, Beall O Patient tolerance to carbonic anhydrase inhibitors *Am J Ophthalmol* 1978, 85: 495–502.

10 Berson F, Epstein D Carbonic anhydrase inhibitors management of side effects *Perspect Ophthalmol* 1980, 4: 91–5

11 Friedland B, Mallonee J, Anderson D Short-term dose response characteristics of acetazolamide in man *Arch Ophthalmol* 1977, 95: 1809–12.

12 Foster TS, Kielar RA, Dipiro JT. Clinical and bioavailability studies of two formulations of acetazolamide. A scientific exhibit Lederle Laboratories, Litho, USA, 1982.

13 Joyce PW. Acetazolamide in primary open angle glaucoma University of Manchester, 1987: MSc thesis.

14 Berson F, Epstein D, Grant W, Hutchinson T, Dobbs P Acetazolamide dosage forms in the treatment of glaucoma *Arch Ophthalmol* 1980, 98: 1051–4

15 Wistrand PJ The use of carbonic anhydrase inhibitors in ophthalmology and clinical medicine *Ann NY Acad Sci* 1984, 424: 609–19

16 Lichter P, Musch D, Medzihradsky F, Standardi L Intraocular pressure effects of carbonic anhydrase inhibitors in primary open angle glaucoma *Am J Ophthalmol* 1989, 107: 11–7

17 Maclure GM, Vogel R The effect on diurnal control of IOP of co-administration of pilocarpine and Timoptol an interim report *Res Clin Forums* 1985, 7: 85–91

18 Hass I, Drance SM Comparison between pilocarpine and timolol on diurnal pressure in open angle glaucoma *Arch Ophthalmol* 1980; 98: 480–1

British Journal of Ophthalmology, 1990, 74, 417–420

Outcome of iatrogenic choroidal neovascularisation in sickle cell disease

Peter D Fox, Robert W Acheson, Graham R Serjeant

Abstract

Choroidal neovascularisation developed in 62/66 (94%) eyes followed up for a mean period of 11·2 years after treatment with xenon arc feeder vessel coagulation for proliferative sickle retinopathy (PSR). In 27 eyes the neovascularisation was chorioretinal alone and in 35 eyes choriovitreal. Chorioretinal neovascularisation (CRN) was a benign complication but may convert to choriovitreal neovascularisation (CVN). Late sequelae of CVN included vitreous haemorrhage, posterior vitreous face fibrosis, and tractional retinal detachment. Visual loss (of ≥ 3 Snellen lines for ≥ 3 months) occurred in nine eyes affected by choroidal neovascularisation, though because of other pathology this could not always be attributed to the choroidal neovascularisation. The incidence of visual loss in CVN affected eyes was significantly greater, by survival curve analysis, than in eyes affected by CRN alone. Permanent visual loss from tractional retinal detachment definitely attributable to CVN occurred in 2/35 (6%) eyes.

Treatment of proliferative sickle retinopathy (PSR) by feeder vessel coagulation achieves closure of the new vessels in most patients.[1] Choroidal neovascularisation at the coagulation site is a serious complication of feeder vessel treatment because of the risk of subsequent vitreous haemorrhage or retinal traction.[2,3] However, the long term risk to visual function is unknown, and the experience with iatrogenic choroidal neovascularisation in 62 affected eyes monitored for a mean period of 11·2 years is therefore reported.

Patients and methods

Patients treated were in two consecutive trials of xenon arc feeder vessel coagulation of proliferative sickle retinopathy at the Sickle Cell Clinic, University of the West Indies, and were invited to attend for further review. They were enrolled between March 1973 and January 1977 in a nonrandomised trial[4] which assessed coagulation of both the feeding arteriole and the new vessels, and in a controlled randomised trial[5] between April 1978 and September 1980 of coagulation of the feeding arteriole only. Of the 103 treated patients 29 were known to have emigrated, four had died, and 13 could not be traced. In the remaining 57 patients who attended for review there were 66 treated eyes of which 31 were treated in the first trial and 35 in the second. There were 40 patients with sickle cell-haemoglobin C (SC) disease, 12 with homozygous sickle cell (SS) disease, three with sickle cell-beta$^+$ thalassaemia, and two with sickle cell-beta^0 thalassaemia.

The most recent assessment in 1988 included ocular symptoms, corrected acuities, fundal examination, and fluorescein angiography. The previous notes and angiograms were reviewed to determine the type, onset, and behaviour of any choroidal neovascularisation. These abnormal vessels may remain in the plane of the chorioretinal scar (CRN) or may extend into the vitreous (CVN). The mean follow-up of all 66 eyes from initial treatment until review in 1988 or until an eye had no perception of light was 11·2 years (range 7·5 to 15·4 years, except for one eye which had reached no perception of light after 3·2 years' follow-up). Visual loss was defined as a decrease in acuity of 3 or more Snellen lines for three or more months (using Snellen lines 6/6, 6/9, 6/12, 6/18, 6/24, 6/36, 6/60).

Results

Choroidal neovascularisation developed in 62/66 treated eyed (94%). CRN alone developed in 27 eyes and both CVN and CRN in 35 eyes. A total of 173 CRN lesions were identified in 62 eyes (range 1–6 per eye) and 70 CVN lesions in 35 eyes (range 1–4 per eye, involving 10–120° circumferentially).

Age, sex, genotype, and trial protocol did not influence the type of choroidal neovascularisation that developed, and no features distinguished the four eyes that did not develop choroidal neovascularisation. The mean age of all patients at initial treatment was 33·8 years (range 13·2–67·1 years).

Nine patients received bilateral treatment, of whom eight developed choroidal neovascularisation (unilateral CVN in one, bilateral CRN in two, bilateral CVN in two, and CRN in one eye and CVN in the other in three patients).

OPHTHALMOSCOPIC AND ANGIOGRAPHIC APPEARANCES

On ophthalmoscopy CRN appeared as a dirty white membrane within a coagulation scar and was usually surrounded by hyperpigmentation. CVN was whiter, more fibrous, and extended up in to the vitreous, often overlying anterior untreated retina.

On fluorescein angiography of CRN a fine vessel system could often be identified in early phases of the study (Fig 1A), but the characteristic finding was of hyperfluorescence confined to the coagulation scar in later phases of the study (Fig 1B). CVN usually showed a typical arborescent pattern in early phases of the angiogram (Fig 2A) which leaked profusely in later phases

Medical Research Council Laboratories (Jamaica), University of the West Indies, Mona, Kingston 7, Jamaica
P D Fox
R W Acheson
G R Serjeant

Correspondence to Professor G R Serjeant, Medical Research Council Laboratories, University of the West Indies, Kingston 7, Jamaica, West Indies.

Accepted for publication 26 January 1990

Figure 1: Superotemporal region of left eye in a 21-year-old female with SC disease with chorioretinal neovascularisation developing 1–18 months after treatment. (A) Early phase. (B) Late phase.

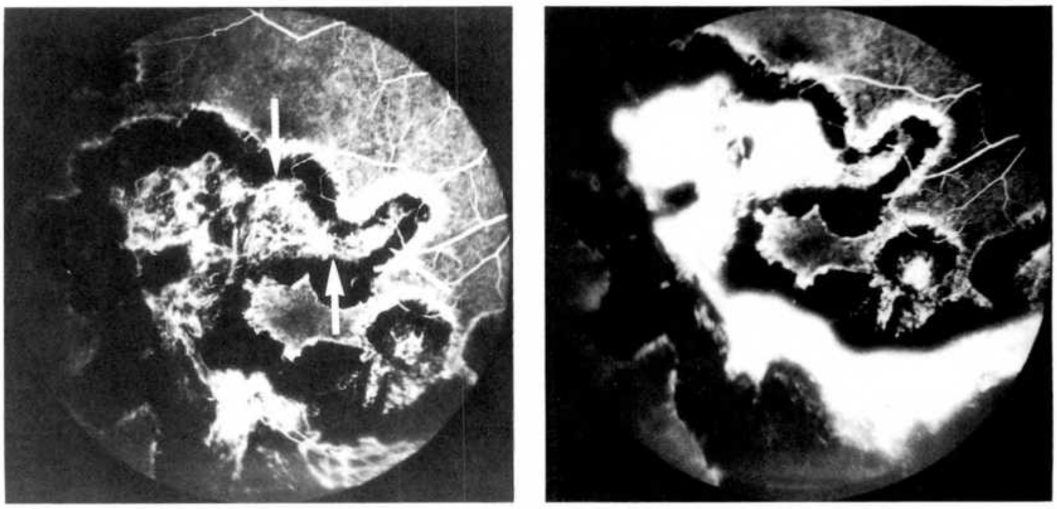


Figure 1A *Figure 1B*

of the study (Fig 2B). The CVN feeding vessels usually passed through an area of CRN.

ONSET AND FOLLOW-UP OF CHOROIDAL NEOVASCULARISATION

The mean time interval between treatment and diagnosis was 1·3 years for CRN (in all 62 eyes developing choroidal neovascularisation) and 3·8 years for CVN. Chorioretinal neovascularisation was observed within one year of treatment in 37/62 eyes (60%) and within 35 days in one eye. Choriovitreal neovascularisation developed in 6/35 eyes (17%) in the first year and was first observed at 60 days in one eye. Most CVN developed between one and three years after treatment, though the observed interval was up to 7·8 years. The mean follow-up from the diagnosis of choroidal neovascularisation to last assessment was 9·9 years for CRN and 7·4 years for CVN.

GROWTH AND REGRESSION

Of the 173 CRN lesions identified in 62 eyes 25 (in 16 eyes) were CRN/CVN complexes when first observed. During follow-up a further 41 CRN lesions (in 25 eyes) converted into CRN/CVN complexes, of which one followed xenon arc photocoagulation of a CRN lesion. Only four CVN lesions (in four eyes) did not have identifiable associated CRN. Of the 70 CVN lesions (in 35 eyes) angiograms adequate to assess behaviour were available for 57 lesions (in 30 eyes), of which 15 (in 10 eyes) enlarged 11 (in 9 eyes) regressed, nine (in 6 eyes) initially grew and later regressed, and 18 (in 13 eyes) remained stable on follow-up. There was no difference in length of follow-up of lesions manifesting growth, regression or stability. Xenon arc photocoagulation of the remaining four CVN lesions in three eyes (misdiagnosed as PSR) resulted in non-perfusion of all four, but subsequently three became reperfused and one remained non-perfused 7·2 years later. Growth of CVN lesions (Figs 3A, B) usually occurred in the two years following diagnosis, though it did occur between 5·8 and 6·3 years later in one lesion. Of the 20 CVN lesions showing spontaneous regression, this proceeded to non-perfusion in seven CVN lesions over intervals of 1·6–5·7 years from diagnosis, and haemorrhage into the CVN preceded regression in four lesions.

VITREOUS HAEMORRHAGE

Vitreous haemorrhage occurred in 19 eyes and

Figure 2: Superotemporal region of right eye in a 32-year-old female with SS disease with choriovitreal neovascularisation developing 19–24 months after treatment. (A) Early phase. (B) Late phase.

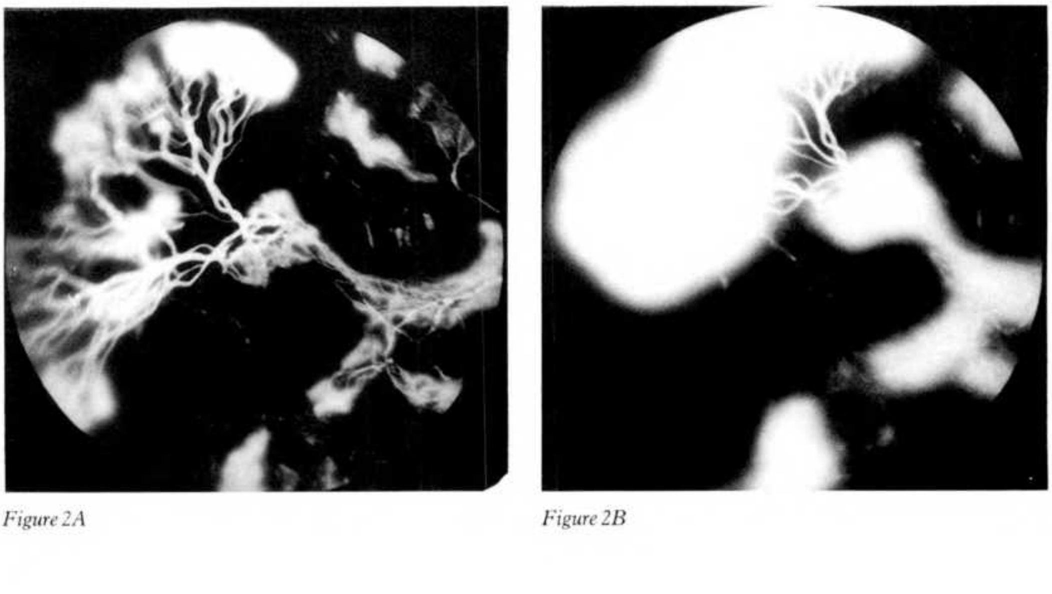


Figure 2A *Figure 2B*

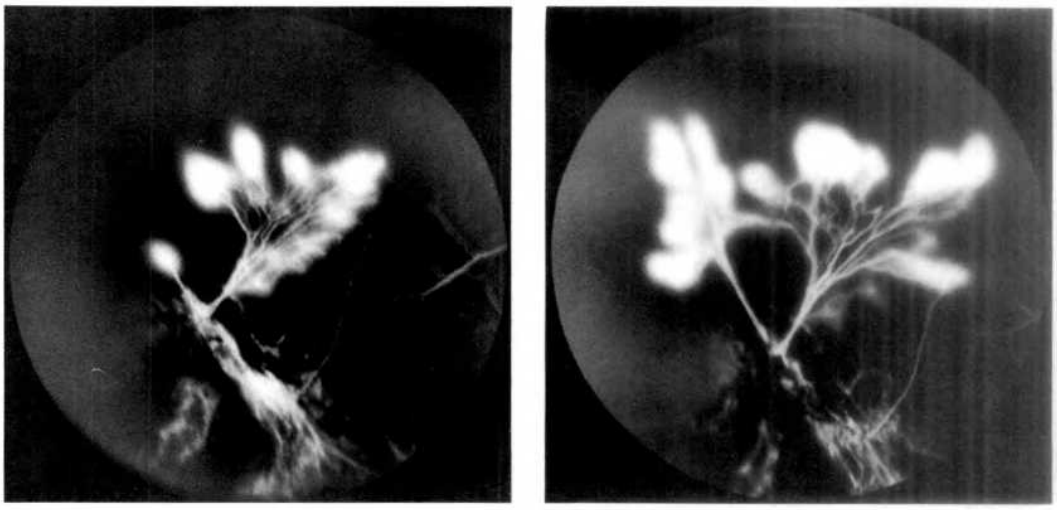


Figure 3: Superior region of right eye in a 43-year-old male with SC disease with chorioviitreal neovascularisation 3·4 years after treatment. (A) One year after diagnosis of CVN. (B) One year later showing spontaneous growth.

Figure 3A

Figure 3B

could be traced to CVN in 14 eyes and to PSR in three. The remaining two eyes had both CVN and PSR, either of which could have been the source. Vitreous haemorrhage was recurrent in 8/14 CVN eyes. Haemorrhage sufficient to cause visual loss occurred in only four eyes (three with CVN, one with both CVN and PSR) and occurred 1·6–11·9 years after treatment. Vitreous haemorrhage not affecting vision occurred up to 15 years from treatment. No vitreous haemorrhages were associated with CRN.

RETINAL DETACHMENT

In 11 eyes with CVN and one eye with both CVN and PSR the detached or partially detached posterior vitreous face was fibrosed with peripheral attachments to neovascular tissue. Contraction of the posterior vitreous face led to tractional retinal detachments in three eyes with CVN and one eye with both CVN and PSR. Of the three CVN eyes with tractional detachments two lost vision 7·7 years and 13·4 years after treatment, and the third had a localised rhegmatogenous retinal detachment adjacent to CVN tissue as well as a localised posterior pole tractional detachment not affecting vision. The eye with both CVN and PSR developed a tractional detachment with visual loss at 9·2 years.

VISUAL LOSS

Visual loss occurred in nine eyes during the study (Table I). In one eye (case 6) a tractional detachment was preceded by vitreous haemorrhage causing visual loss. In case 8, with both CVN and PSR, the eye became phthisical before ultrasound examination was available, so the presence of a detachment could not be ascertained. Irretrievable visual loss from tractional retinal detachments solely attributable to CVN occurred in two eyes (cases 6 and 7). The incidence of visual loss in eyes with only CRN was 0·3/100 eye years of observation after treatment compared with 2·2/100 eye years of observation in eyes with CVN (including eyes with both CVN and PSR). This difference was significant by survival curve analysis ($\chi^2=4\cdot17$, $p=0\cdot04$). Since CRNs and CVNs develop at different intervals after treatment, reassessments of these incidence rates for the known duration of choroidal neovascularisation gave corresponding figures of 0·4 and 3·1, representing an even greater difference.

TABLE I *Visual loss in eyes with choroidal neovascularisation*

Case	Age at treatment (years)	Sex and genotype	Treatment to visual loss (years)	Visual acuity			Cause of visual loss	Type of new vessels
				Initial	Worst	Final		
1	48	M SS	6·7	6/6	2/60	2/60	Epiretinal membrane	CRN
2	51	M SC	9·6	6/6	6/36	6/36	Epiretinal membrane	CVN
3	28	F SC	12·0	6/6	6/60	6/60	Epiretinal membrane	CVN
4	32	M SC	11·9	6/6	HM	6/12	Vitreous haemorrhage	CVN
5	57	F SS	1·6	6/12	6/60	6/12	Vitreous haemorrhage	CVN
6	38	F SC	9·4	6/6	6/60		Vitreous haemorrhage	CVN
			13·4		NPL	NPL	Tractional detachment	
7	37	M SS	7·7	6/6	6/60	6/60	Tractional detachment	CVN
8	22	M SC	3·2	6/6	NPL	NPL	Vitreous haemorrhage	CVN and PSR
9	44	F SC	9·2	6/6	NPL	NPL	Tractional detachment	CVN and PSR

HM=hand movement. NPL=no perception of light.

Discussion

Choroidal neovascularisation was a common complication of feeder vessel coagulation of proliferative sickle retinopathy, and although occurring more frequently with xenon arc, occurs also with argon laser photocoagulation.[5,6] Choroidal neovascularisation has followed xenon arc and argon laser photocoagulation in diabetic retinopathy[7] usually when new vessels were repeatedly treated by focal photocoagulation using small spot sizes. Choroidal neovascularisation has also been induced by small, intense photocoagulation burns in rhesus monkeys,[8] and histological examination confirmed vasoproliferation through defects in Bruch's membrane. Retinal ischaemia, choroidal ischaemia, and post-photocoagulation inflammation have all been postulated[3] as stimuli for choroidal neovascularisation in sickle cell retinopathy following disruption of Bruch's membrane by photocoagulation. Since the frequency of choroidal neovascularisation did not differ between the two therapeutic protocols employed in the Jamaican studies, it seems unlikely that the more extensive photocoagulation in the first trial was a causal factor.

The development of choroidal neovascularisation in the great majority of patients receiving feeder vessel coagulation for PSR has raised the concern that one neovascular network has been replaced by another which may have an equally bad or possibly worse visual prognosis. Complications from choroidal neovascularisation in sickle cell disease include vitreous haemorrhage, vitreoretinal traction, and tractional retinal detachments,[2,3,9] but the long term risk to visual function remained to be determined. Earlier reports describing short term follow-up were contradictory. In 16 eyes developing CVN, followed up at this unit[2] for a mean period of 3·3 years, increasing retinal traction was observed in one eye, but there was no visual loss. In Chicago[3] 10 eyes developed CVN following argon laser feeder vessel coagulation of PSR, and during a mean follow-up of 4·2 years three developed tractional retinal detachments, two of which involved the macula. However, the same group[9] later described nine eyes with CVN over a mean follow-up of 5·8 years and found no permanent profound visual loss.

Longer term follow-up in the present study indicates that CRN was a benign complication, though conversion to CVN occurred in 41 lesions occasionally several years later. Vitreous haemorrhage from a CVN was common and often recurrent, but visual loss was unusual. Posterior vitreous face fibrosis attached to CVN was a more ominous sign, and progression to tractional retinal detachment and irretrievable visual loss were observed. Visual loss from macular epiretinal membranes was difficult to attribute to CRN or CVN because the complication may follow photocoagulation, vitreous haemorrhage, and PSR itself.[10] The risk of visual loss in the present study was significantly greater in eyes developing CVN than CRN, and the incidence rate of visual loss in CVN eyes was similar to that observed in untreated eyes with PSR in this unit.[11]

This observation indicates that little has been achieved by the treatment of PSR if chorioviitreal neovascularisation develops as a complication. Although it is commoner after xenon arc therapy, this complication also occurs with argon laser photocoagulation, and protocols for treatment by both methods should be changed so as to minimise the risks of development of choroidal neovascularisation.

1 Condon PI, Serjeant GR Photocoagulation and diathermy in the treatment of proliferative sickle retinopathy *Br J Ophthalmol* 1974; 58: 650–62.

2 Condon PI, Jampol LM, Ford SM, Serjeant GR Choroidal neovascularisation induced by photocoagulation in sickle cell disease *Br J Ophthalmol* 1981; 65: 192–7

3 Dizon-Moore RV, Jampol LM, Goldberg MF Chorioretinal and choriovitreal neovascularization. *Arch Ophthalmol* 1981, 99: 842–9

4 Condon PI, Serjeant GR. Photocoagulation in proliferative sickle retinopathy results of a five-year study *Br J Ophthalmol* 1980, 64: 832–40

5 Jampol LM, Condon PI, Farber MD, Rabb M, Ford SM, Serjeant GR A randomised clinical trial of feeder vessel photocoagulation of proliferative sickle cell retinopathy 1. Preliminary results *Ophthalmology* 1983; 90: 540–5

6 Condon PI, Jampol LM, Farber MD, Rabb M, Serjeant GR A randomised clinical trial of feeder vessel photocoagulation of proliferative sickle cell retinopathy. II. Update and analysis of risk factors *Ophthalmology* 1984; 91: 1496–8

7 Chandra SR, Bresnick GH, Davis MD, Miller SA, Myers F Choroidovitreal neovascular ingrowth after photocoagulation for proliferative diabetic retinopathy *Arch Ophthalmol* 1980, 98: 1593–9

8 Archer DB, Gardiner TA Morphologic, fluorescein angiographic and light microscopic features of experimental choroidal neovascularization. *Am J Ophthalmol* 1981, 91: 297–311

9 Carney MD, Paylor RR, Cunha-Vaz JG, Jampol LM, Goldberg MF Iatrogenic choroidal neovascularization in sickle cell retinopathy. *Ophthalmology* 1986, 93: 1163–8

10 Moriarty BJ, Acheson RW, Serjeant GR Epiretinal membranes in sickle cell disease *Br J Ophthalmol* 1987, 71: 466–9.

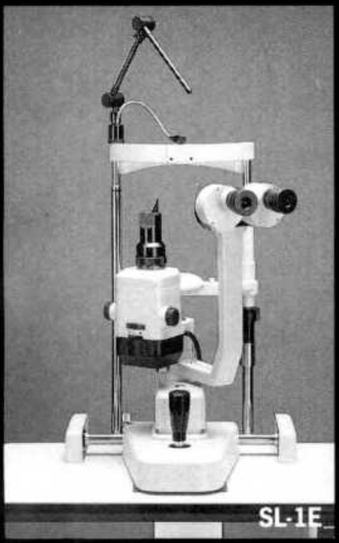
11 Moriarty BJ, Acheson RW, Condon PI, Serjeant GR Patterns of visual loss in untreated sickle cell retinopathy *Eye* 1988; 2: 330–5.

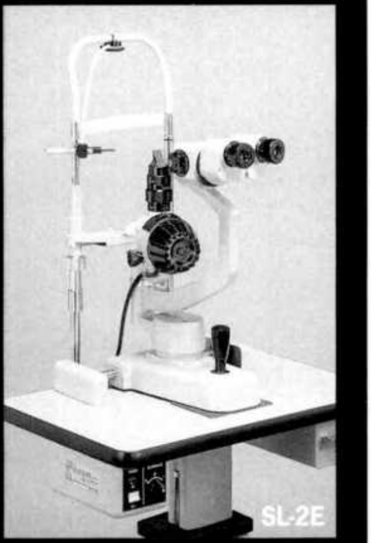
In keeping with our philosophy of supplying only top quality equipment, Keeler are now the exclusive distributors for TOPCON.

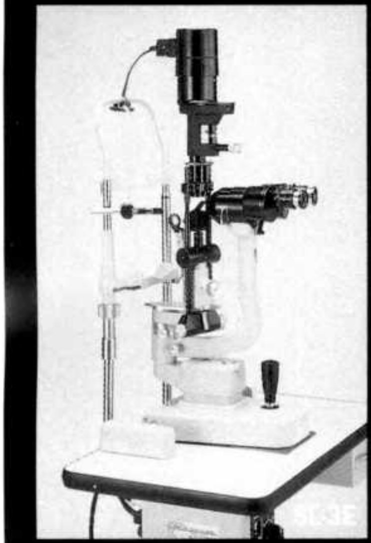
The full range of Topcon slit lamps allows the practitioner to choose exactly the right instrument for his particular needs.

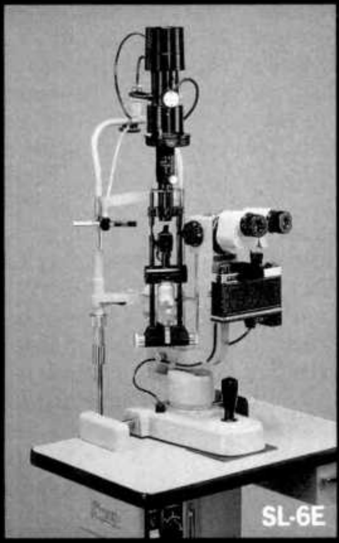
Within the range, Topcon now offers high magnification versions of their most popular slit lamps. These are illustrated opposite, and the details listed below.

If a permanent record is required, then this is achievable with photographic attachments which allow the use of 35mm, Polaroid or, in the case of the SL-6E, video recording.









SL-1E
- 14mm slit illumination
- Omni directional joystick
- Variable magnification capability
- Built-in filters
- Halogen illumination

SL-2E
- Convergent binocular tubes enhance the examination
- Omni directional joystick
- Three-position magnification
- Infinitely adjustable slit width and length
- Built-in filters
- 35mm photographic attachment

SL-3E
- Omni directional joystick
- Two fixation targets
- Convenient, lever-controlled magnification change
- Slit beam inclination
- Four built-in filters
- Infinitely adjustable slit width and length
- Pachometer attachment

SL-6E
- Convergent binocular tubes for unprecedented viewing
- Omni directional joystick
- Five-position magnification
- Four built-in filters
- 35mm photographic attachments
- Polaroid attachment model PA-8S
- Video attachment
- Non-contact specular attachment
- Pachometer attachment
- Observation tube

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

LONDON CENTRE
Keeler Martin and Tomkins, 38 Margaret Street,
Cavendish Square, London W1A 4NS
Telephone: 01-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
Telephone: (0236) 721214 Fax: (0236) 721231

ORMATION

RESENTATION

lear colourless solution in a plastic
pper bottle. Glauline is available in
e strengths containing 0.1%, 0.3%
0.6% w/v metipranolol together
h benzalkonium chloride 0.01%
as a preservative.

SES

auline is a beta adrenoceptor
cking agent used in the topical
atment of chronic open-angle
ucoma and other conditions in
ich intra-ocular pressure is elevated
ve normal levels.

OSAGE AND MINISTRATION

recommended dosage is one drop
illed into the affected eye(s) twice
[redacted] diagnosed patients with
pertension or chronic
glaucoma should be treated
the first instance with Glauline
%, changing to a higher strength if
equate control of intra-ocular
ssure is not achieved or maintained.
ients on existing therapy, whether
not this is to be continued, should
ive Glauline 0.3%. Glauline 0.6%
uld be reserved only for patients
ose intra-ocular pressure is not
quately controlled with 0.3%
uline and for whom the prescribing
sician does not wish to add
litional therapy. Patients with
ucoma should not be treated with
% Glauline as initial therapy.

ONTRA-INDICATIONS, RNINGS, ETC

use of Glauline is not
ommended in patients with
tructive airways disease, cardiac
lure or hypersensitivity to
ipranolol. Beta blockers should
be given with verapamil and
her drug should be administered
hin several days of discontinuing
othe[redacted]As absorption into the
ulatio possible, Glauline should
be used with caution in patients
ady receiving similar drugs by
th or where systemic use of beta
ckers is contraindicated. In
icular, care should be taken in
ents with sinus bradycardia and
ater than first degree heart block.
hough there is no evidence to
gest that metipranolol has
ogenic properties, its use during
gnancy should be avoided, unless
potential benefits are considered to
weigh the possible hazards. No
ical trials in children have been
ied out. Glauline should not be
d in patients fitted with soft
drophilic) contact lenses. There
e been a small number of reports of
s of granulomatous anterior uveitis
uring in elderly patients using 0.6%
uline. In any case where a patient
ws symptoms or signs suggestive
nterior uveitis, Glauline should be
hdrawn and an alternative ocular
otensive agent substituted.

IARMACEUTICAL ECAUTIONS

uline should not be diluted or
pensed from any container other
the original bottle. The unopened
duct has a shelf life of 3 years, but
with other eye drops the contents of
h bottle should be discarded one
nth after opening.

EGAL CATEGORY - POM

ACKAGING QUANTITIES

uline is supplied as a sterile
thalmic solution in a 5ml plastic
pper bottle.

URTHER INFORMATION

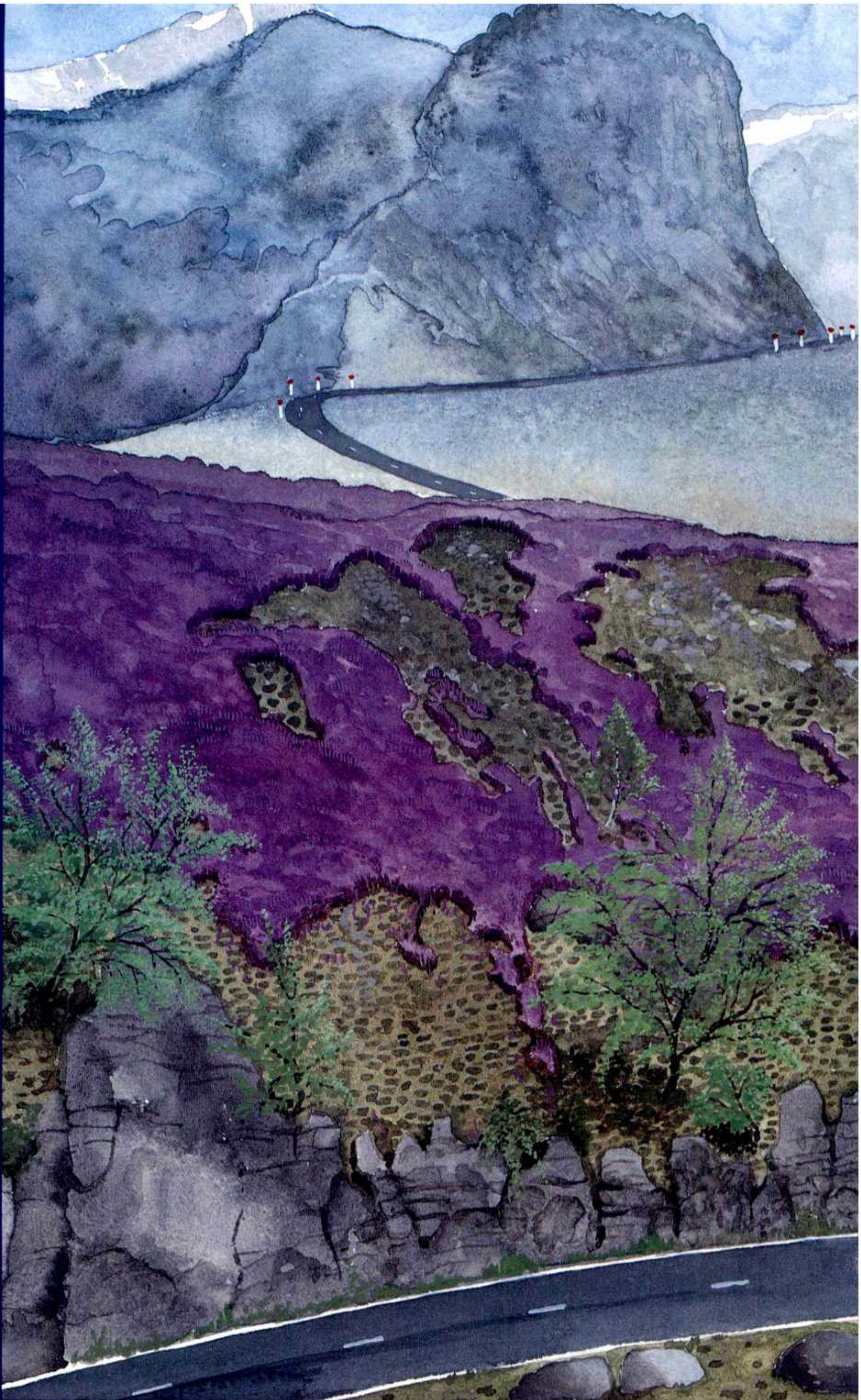
uline has little or no effect on pupil
or accommodation. Glauline is
erally well tolerated but some
ients may complain of a slight
ging which soon passes off.
nsient headaches have also been
orted.

RODUCT LICENCE MBERS

uline 0.1% 0033/0104
uline 0.3% 0033/0105
uline 0.6% 0033/0106

ASIC NHS PRICE

- 0.1% £4.03, 0.3% £4.67, 0.6%
05



Glauline*

METIPRANOLOL

*Trade Mark

Smith & Nephew Pharmaceuticals L

Bampton Road, Harold Hill
Romford, Essex, RM3 8SL, England
Telephone: 04023 49333
Telex: 898058 SMINEPG
Fax: 04023 71316

BASCOM PALMER EYE INSTITUTE
MIAMI, FLORIDA

XII INTERAMERICAN COURSE

an advanced course in clinical ophthalmology

November 6–10, 1990*

Pediatric Ophthalmology
Uveitis
Cataract/IOL
Recent Advances
External Disease
Glaucoma
Contact Lenses
Elective Practical Courses

* Week after American Academy meeting

Course Fee ($U.S.)

Before November 1	**$300.00**
After November 1	**$400.00**

Application form and details from:

Interamerican Course
Bascom Palmer Eye Institute
P.O. Box 016880
Miami, Florida 33101, U.S.A.

UNIVERSITY OF LONDON

INSTITUTE OF OPHTHALMOLOGY

Associated with MOORFIELDS EYE HOSPITAL

The following Courses have been planned:

1990		
2nd-20th July	MCOphth/DO Modular Refresher Course (per week) (3 modules of 1 week each)	£200 £550
10th-28th September	FRCS Final Refresher Course	£400
3rd-5th October	Topics Symposia in Contact Lens Practice	£235
12th-16th November	General Practitioners Course	£200
19th-23rd November	Moorfields Macular Course	£325
3rd-21st December	MCOphth/DO Modular Refresher Course (per week) (3 modules of 1 week each)	£200
1991		
14th-19th January	Paediatric Ophthalmology Course	to be announced

Applications for all courses should be made to the

Dean's Office, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT

British Journal of Ophthalmology, 1990, 74, 421–426

The eye in the CHARGE association

I M Russell-Eggitt, K D Blake, D S I Taylor, R K H Wyse

Abstract

CHARGE association includes patients with at least four features prefixed by the letters of the mnemonic: Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies and/or hearing loss. Many also have facial palsy. We report a series identified by collaboration within one centre of all specialties concerned in the management of the CHARGE association. Ocular abnormalities were found in 44 out of 50 patients with the CHARGE association. Of these, 41 had 'typical' colobomata. The majority had retinochoroidal colobomata with optic nerve involvement, but only 13 patients had an iris defect. Two patients had atypical iris colobomata with normal fundi. Additional features were microphthalmos in 21 patients, optic nerve hypoplasia in four, nystagmus in 12, and a vertical disorder of eye movement in four of the 22 cases with facial palsy. We report an incidence of coloboma in the CHARGE association of 86% (43/50) compared with a previous cumulative reported incidence of 66% (112/170). We believe that there may have been previous underdiagnosis of colobomata in children with multiple congenital abnormalities.

Among the myriad of congenital abnormalities seen in paediatric practice the grouping of cases where certain features often occur in association is useful and often precedes understanding of the aetiology.

The CHARGE association includes patients with at least four features prefixed by the letters of the mnemonic: Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia. Ear anomalies and/or hearing loss.[1] The diagnosis has become more specific as patients with this phenotype but with a known aetiology, such as cat-eye syndrome (partial tetrasomy 22), Di-George syndrome (deletion 22q11), and multiple abnormalities due to teratogens such as retinoic acid, are excluded.

Most cases of CHARGE seem to be sporadic. Environmental or genetic causes may act similarly. Autosomal dominant pedigrees of CHARGE give support to a genetic basis in a minority of patients.[2-5] The similarities between patients are striking, and there is considerable concordance within dominant pedigrees. In 1981 Pagon *et al*[1] described this non-random series of features comprising CHARGE association in order that later splitting by aetiology might be possible. Since then it has become clear that facial palsy, renal abnormalities, orofacial clefts, and tracheo-oesophageal fistulae also frequently accompany the main features.[6]

Warburg has suggested that the VACTERL association (vertebral malformation, atresia of the anus, cardiac malformation, trachael fistula, oesophageal atresia, renal and radial dysplasia, and limb malformations) may be an expression of the same defect as the CHARGE association.[7]

Pagon *et al*[1] and subsequently several other authors[8 9] have included in the CHARGE association cases of the Di-George syndrome. This is a disorder in development of the third and fourth pharyngeal pouches, with parathyroid and thymic hypoplasia, cleft palate, micrognathia, low-set ears, and heart defects,[10] now known sometimes to be due to a deletion in the region 22q11 of chromosome 22.

Davenport *et al*[11] reported a series of 15 patients with the CHARGE association, with a similar multidisciplinary ascertainment to our study. In many other reports of the CHARGE association there is a bias towards certain abnormalities: the 17 cases described by Hall were selected on the basis of choanal atresia and multiple abnormalities.[12] Pagon *et al*[1] described 21 patients all of whom had choanal atresia and/or colobomata. In the most recent review of the CHARGE association Chestler and France[13] added six further cases with a bias towards colobomata.

In this paper we report the incidence and range of ocular features in the CHARGE association. Our aim was to record the largest series to date and to reduce bias of ascertainment by collaboration, within one centre, of all specialties concerned in the management of the CHARGE association.

Patients and methods

This study describes the ophthalmic features of 50 patients with the CHARGE association all of whom have been seen at one centre. Ascertainment of patients, both retrospective and prospective, was through a variety of specialists: a general paediatrician, geneticist, cardiologist, otorhinolaryngologist, and ophthalmologist. Most cases presented as neonates requiring major surgery for congenital heart disease, choanal atresia, or tracheo-oesophageal fistula. Patients with CHARGE features were screened during this study, if not previously, by all the specialists for further features. The minimum criterion for inclusion in our study required that patients should have at least four of the major features in the acronym.[11] There were 28 males and 22 females. There were 13 deaths, most during the first year of life; those who died had all undergone at least three non-ophthalmic surgical procedures.

The six major systemic features of CHARGE are presented in Table I. Facial palsy was also included as a major feature, as it has been previously reported in at least 40 cases and is an otherwise uncommon finding in infancy.[14]

Department of Ophthalmology, Hospital for Sick Children, Great Ormond Street, London
I M Russell-Eggitt
D S I Taylor

Department of Paediatric Cardiology, Institute of Child Health, 30 Guilford Street, London WC1
K D Blake
R K H Wyse

Correspondence to
D S I Taylor, FRCP, FRCS,
Hospital for Sick Children,
Great Ormond Street, London
WC1N 3JH

Accepted for publication
26 January 1990

TABLE I *The initial letters of the acronym CHARGE are used to denote features present in each case reported*

*C*oloboma
*H*eart defect
*A*tresia of choanae
*R*etardation of growth or development
*G*enital hypoplasia
*E*ar abnormalities or deafness
*p*alsy of facial nerve

1	CHARGEp	26	H RGEp
2	CHARGE	27*	CHAR E
3*	C AR Ep	28	CHARGEp
4*	CHAR E	29	CH RGE
5	CHARGEp	30	CH RGE
6	C RGE	31*	CHAR Ep
7	CH R Ep	32*	CH R Ep
8	CH RGE	33*	C AR E
9	CH RGEp	34	CH RGE
10	CHA GEp	35	CH RGEp
11	HARGE	36*	CHAR Ep
12*	CHA E	37*	CHAR Ep
13	CHA GEp	38*	CHAR E
14	C RGEp	39	CH RGEp
15	CHARGE	40*	CH R E
16*	CHAR E	41	H RGEp
17	CHARGEp	42*	CH R E
18	C ARGE	43	CH RGE
19*	CHAR Ep	44*	CH R E
20*	CHAR Ep	45*	HAR E
21	CH RGEp	46*	HAR E
22	CHARGE	47*	CH R E
23*	HAR E	48	CH RGE
24*	CHAR Ep	49	CH RGE
25	CHARGE	50*	C AR E

*Denotes female.

Genital abnormalities were apparent only in the males.

Results

KARYOTYPES

Chromosome analysis was performed in 48/50 of the patients and an abnormality in blood chromosomes was confirmed only in case 36, which had an apparently balanced translocation of chromosomes 6 and 8.

OCULAR FINDINGS

The ocular features of the individual patients are summarised in Table II. Ocular abnormalities were found in 44/50 patients (88%); 41 (82%) of these had a 'typical' coloboma of varying severity. Two patients had atypical iris colobomata with normal fundi: case 8 had a unilateral upper nasal defect and case 48 had bilateral nasal defects.

TABLE II *The frequency of occurrence of major ocular features is tabulated*

	Number of patients			
	Right	*Left*	*Bilateral*	*Total*
Colobomata				
Iris	5	2	6	13
Retinochoroidal	7	3	30	40
Optic disc	4	6	27	37
Eyelid				1
Microphthalmos	7	6	8	21
Squint				17
Nystagmus				12

Colobomata affected the posterior segment in 38/50 cases (bilateral in 32). Two additional cases had gross microphthalmos of the fellow eye, and in all but seven eyes the optic disc was involved.

In some cases the coloboma was very subtle, but nonetheless of diagnostic importance: three patients had iris colobomata which involved only part of the stroma, and two patients with posterior colobomata had only a small defect in the retinal pigment epithelium just below and nasal to the optic disc. The optic disc in these patients had a hyperpigmented border, especially temporally, and in one eye this was the only abnormality, but the fellow eye had a disc coloboma with inferonasal chorioretinal thinning with scleral ectasia (Figs 1A, 1B).

Microphthalmos was bilateral in eight patients, right sided in seven, and left in six, but was mild in the majority. Only one eye of three patients had no useful vision.

Optic nerve hypoplasia was noted in patients 19, 30, 41, and 50. In all these cases the eye with the hypoplastic disc was the better seeing eye, with an acuity range of 6/6-6/18. Only patient 50 had a pigmented optic disc border, and none had the double pigmented ring sign of optic nerve hypoplasia.

Two patients (17 and 41) had unilateral persistent hyperplastic primary vitreous (without a fundal view), case 17 had a 'typical' coloboma (that is, occurring along the embryonic fissure), while case 41 had hypoplasia of the fellow optic disc. Patient 47 had partial upper lid colobomata, and two cases (9 and 47) had blockage of the nasolacrimal duct.

One patient (18) had cataract in association with retinal detachment, and case 17 had spon-

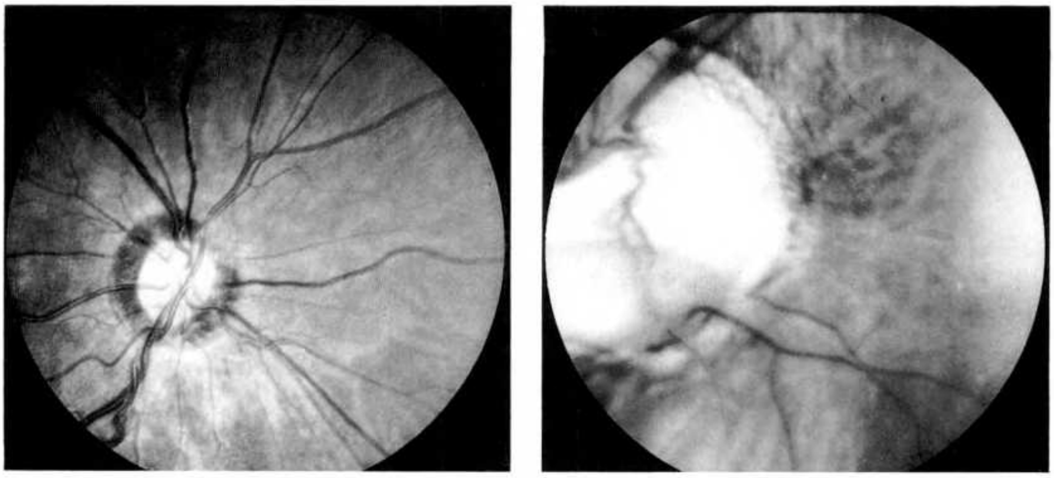


Figure 1: The right optic disc of case 50 has a hyperpigmented border, the visual acuity is 6/6 with a −3·00 dioptre sphere. The fellow optic disc is colobomatous with inferonasal chorioretinal thinning and scleral ectasia. The acuity is 6/36 with −12·00 dioptre sphere.

Figure 1A

Figure 1B

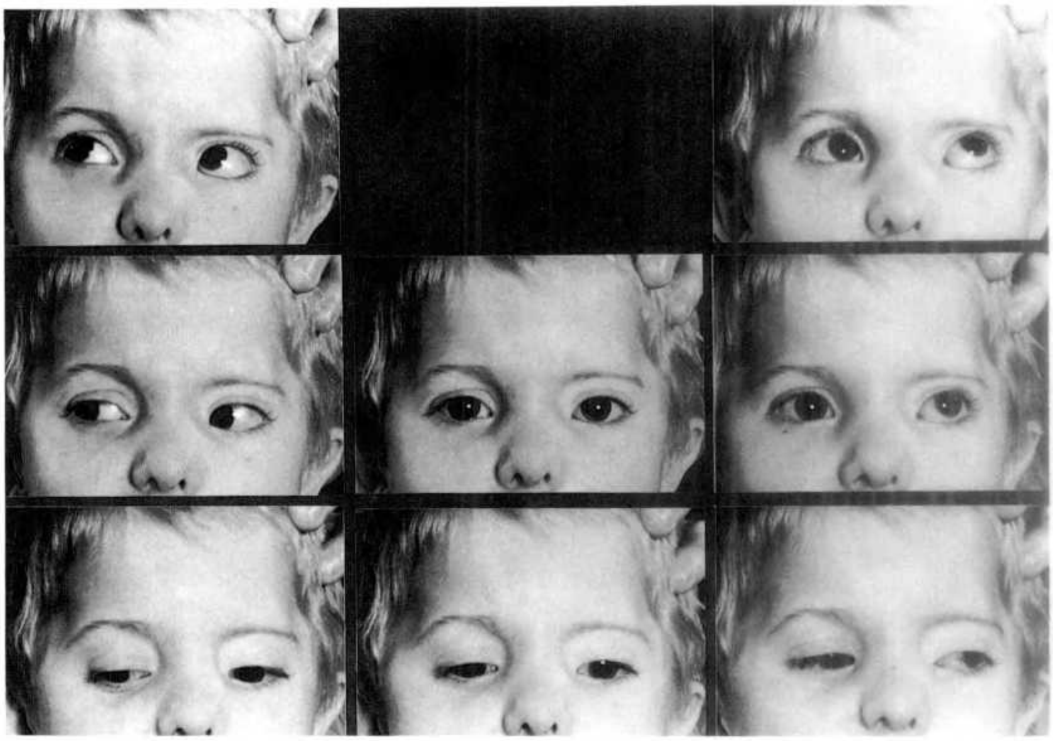


Figure 2: The right eye of case 19 fails to elevate fully, especially in adduction, and the left eye shows apparent overaction in laevoelevation. The left eye is mildly microphthalmic, with inferior corneal scarring due to facial nerve weakness.

taneous dislocation of the lens. In case 25 there was a unilateral anterior polar lens opacity. Strabismus was present in 17 patients: seven esodeviations, eight exodeviations, and two which were initially convergent but became divergent.

Nystagmus was seen in 14 (28%). All of these had optic disc colobomata except for case 7, which had pallor of the retinal pigment epithelium only inferonasal to normal optic discs. The nystagmus was horizontal except in cases 2, 27, and 49. In cases 2 and 27 it was rotary, with profound hearing loss also present, while in case 49 the eye movements were initially chaotic, later settling, with bursts of vertical nystagmus.

In four cases (5, 9, 19, and 39) there was a disorder of vertical eye movement associated with facial palsy, with deficiency of upgaze, particularly in adduction, of the eye contralateral to the facial nerve weakness (Fig 2). Facial palsy was present at birth or noted soon afterwards in 22 cases (13 right, seven left, and two bilateral). One additional patient, case 3, had hemifacial spasm which resolved. Twenty-one of our patients with facial palsy had a strong Bell's reflex and copious tear formation. Cases 5, 35, and 49 had corneal exposure, with scarring, requiring lateral tarsorrhaphy in spite of simple eye ointment application.

Case 7 had a saccade palsy or oculomotor apraxia, and case 5 had a jaw winking ptosis of Marcus-Gunn type. Cases 1, 19, 32, and 39 had narrow palpebral apertures ipsilateral to microphthalmos. Case 27 had bilateral asymmetrical ptosis, normal sized eyes, and poor levator function which required an internal sling operation on the worse affected side.

Patients 10, 12, 20, 29, 32, 36, and 49 were initially thought to be blind, with no apparent fixing or following, and 'chaotic' eye movements. In all these cases there were bilateral optic disc and extensive chorioretinal colobomata. All these patients improved in visual behaviour. Nystagmus developed in patients 12, 20, and 49.

Thirty-six patients had their refraction estimated. Of these 19 were myopic, eight were hypermetropic, nine were emmetropic, and 14 had more than 2 dioptres of astigmatism. The Snellen acuity was recorded in only 12 cases, the remainder being too young or mentally retarded. One patient had an acuity of 2/60, and another had 2/36 in the better eye; the remainder of patients ranged from 6/5 to 6/18 in their better eyes. There was no correlation between the severity of ocular defect and mental handicap. A more severe visual defect, even absence of light perception, was suspected in some patients with optic disc colobomata.

Discussion

The major ocular feature of the CHARGE association is coloboma. The reported incidence is influenced both by ascertainment and by examination (most colobomata affect the posterior segment alone and some may be subtle defects). We report an incidence of 86% (43/50) compared with a previous cumulative reported incidence of 66% (112/170).[1-8 11-13 15-24] In some studies not all cases were examined by an ophthalmologist, and as posterior colobomata often occur without an iris defect (30/50 in our series) they may have been under-reported. Subtle defects in the retinal pigment epithelium or iris transillumination defects along the presumptive line of the fetal fissure accounted for five of our cases and could easily have been overlooked if colobomatous defects were not being specifically sought.

In our series a grossly hyperpigmented optic disc border was observed both with and without hypopigmented retinal pigment epithelium (cases 38 and 50). This hypopigmentation occurred along the presumptive line of the embryonic fissure. In case 50 the fellow eye had a typical disc coloboma (Fig 1). Such an optic disc appearance has been described previously in a family with microphthalmos and clinical anophthalmos, but without typical coloboma.[25] As microphthalmos is acknowledged as being often associated with coloboma, this adds to the case for 'hyperpigmented optic disc border' sharing a similar aetiology. The peripapillary hyperpigmentation observed in our patients may be associated with anomalous closure of the superior end of the fetal fissure.

The majority of colobomata in our series were typical in that they were fetal fissure defects. In the embryo during the invagination of the optic vesicle a groove (the embryonic fissure) remains open at the inferior aspect of the optic cup, allowing entry of paraxial mesoderm which later forms the hyaloid system. At 4–5 weeks the fissure begins to close centrally, with apposition extending anteriorly and posteriorly by 6 weeks. We observed the complete spectrum of defects previously described,[1 3 11 13] encompassing iris to chorioretinal coloboma with or without optic disc involvement and microphthalmos. Visual acuity ranged in our series from light perception to 6/5 Snellen.

Horizontal pendular nystagmus in the CHARGE association in two of six cases with colobomata has been reported by Chestler and France.[13] In these cases it may be secondary to macular or optic nerve involvement in a coloboma. We propose that nystagmus may also be central in origin. We found our case 7 to have horizontal nystagmus, no major eye defect, and inner ear abnormalities. Furthermore, we found vertical or rotary nystagmus in three patients.

We describe a vertical disorder of eye movement in 4/22 cases with facial palsy, characterised by defective elevation of the globe, with the characteristics of either 'superior oblique muscle overaction' or, in one case, of 'superior rectus underaction'. Traction test has not been possible in all cases to exclude a mechanical limitation of glove movement. However, central disorders of ocular motility are not unexpected in a syndrome in which congenital facial palsy and disorders of swallowing are major features. Vocal cord paralysis has also been reported.[15]

Few cases of ptosis have been reported in the CHARGE syndrome, and most of these are probably pseudoptoses associated with microphthalmos or orbital asymmetry.[16 22 24] Patient 27, with true ptosis, phenotypically resembled Turner's syndrome but had normal chromosomes. August *et al*[22] reported one case of ptosis which may have been central in origin and who also had a disorder of eye movement, but no mention of ocular size was made.

Facial palsy has been previously reported in the CHARGE association,[1 11] but as we add a large number of cases, 22/50 (44%), it may be arguably included as one of the major diagnostic features.

Delayed visual maturation (DVM) has been reported in infants who are severely ill from various causes, including tracheo-oesophageal fistula and chest infection,[26] and in cases with an ocular disorder such as cataracts,[26] albinism,[27] and retinal coloboma.[11] Seven of our patients had DVM and all had bilateral optic disc and chorioretinal colobomata. All required major surgery as neonates; two of them had tracheo-oesophageal fistula, two had laryngomalacia and Nissen's fundoplication.

Our two cases of atypical iris coloboma occurred without posterior segment coloboma. This supports the view that these are not related to a defect in closure of the fetal fissure. François[28] considered them to be a partial aniridia due to a notch at the margin of the optic vesicle.

Case 47 had notches between the inner third and outer two-thirds of the margin of the upper eyelid. This has not been previously reported in the CHARGE association. Other reported cases of lid coloboma[18 20] do not offer sufficient clinical information to determine whether patients had the CHARGE phenotype. Upper lid colobomata are a well described feature of the Goldenhar-Gorlin syndrome,[29] while lower lid defects occur in the Treacher Collins syndrome.[30]

Persistent hyperplastic primary vitreous, seen in two of our cases, has been described in association with coloboma in trisomy 13,[27] which shares many other features with CHARGE.

In the present series as in cases reported elsewhere there is a notable absence of other ocular abnormalities, such as anterior segment dysgenesis and primary cataracts (only case 25 had a primary lens opacity).

Ho *et al*[24] described a mother and her two children with cataract, but they had only 'CH' of CHARGE, and the pregnancy was complicated by diabetes. Their case 5 may have had CHARGE with cataract, as did case II-1 reported by Davenport *et al*,[11] though this patient may have had cataract secondary to retinal detachment. Retinal detachment has been reported in association with posterior colobomata and aphakia in patients with the CHARGE association.[4 11] This emphasises the need for specialist initial eye examination with regular follow-up.

We excluded one patient from our series who had facial palsy and all of the acronymous features of the CHARGE association except for choanal atresia, as chromosome analysis showed him to be trisomic for a part of chromosome 22: the cat-eye syndrome. The phenotypes of the

TABLE III *The phenotypes of syndromes which resemble CHARGE association are tabulated with, where possible, an indication of the frequency of occurrence of individual features*

	CHARGE	*CAT EYE*[33-34]	*GOLDENHAR*[29 35]	*VACTERL*[4 5]	*DI GEORGE*[1 8 10]	*EDWARDS*[28]
Heart defect	***	***	*	***	***	***
Ear anomaly	***	***	***	*	***	**
Coloboma	***	***	*		*	**
Atresia choanae	***	**		*		
Genital anomaly	**		*	*	R	***
Retardation	**	*	*			***
Cleft lip/palate	*	*	*	*	*	*
Renal anomaly	*	***	*	**		*
Vertebral anomaly	*	*	**	**	*	*
Anal atresia	*	**		**		*
Thymus deficient		R			***	*

***Very often (>50%)
**Often (>30%).
*Occasional (>5%)
R=Reported

TABLE IV *Reported ocular features in syndromes with systemic features in common with the CHARGE association*

	CHARGE	CAT EYE[32]	GOLDENHAR[29]	VACTERL[33]	DI GEORGE[1]	EDWARDS[34]
Coloboma	*	*	*		*	*
PHPV	*					
Epibulbar dermoids			*			
Lid coloboma	*		*			
Ocular motility disorder	*		*			
Optic nerve hypoplasia	*		*			

cat-eye syndrome and the CHARGE association are remarkably similar (see Table III). Some patients reported as CHARGE (including some in our series) may be mosaics for cat-eye or have a small deletion of chromosome 22 as in Di-George syndrome. Mosaics with normal blood chromosomes have been reported in full trisomy 22,[31] the abnormality being only detected on fibroblast culture.

Our case 36 with an apparently balanced translocation may provide the cytogenetic clue leading to the identification of a submicroscopic deletion which could be the cause of other cases at present diagnosed as having the CHARGE syndrome with overtly normal chromosomes.

Ocular features may help to separate the different phenotypes of Di-George, VACTERL, cat-eye, and Goldenhar-Gorlin syndromes which have systemic characteristics in common with CHARGE (see Tables III and IV).

CONCLUSIONS

In a large series with the CHARGE association, we have described the spectrum of coloboma-microphthalmos including subtle defects such as a pallor of the retinal pigment epithelium inferonasal to the optic disc and marked peripapillary pigmentation. Ocular motility disorders of central origin also occur frequently; nystagmus may be horizontal, vertical, or rotary. Facial nerve palsy may be accompanied by a vertical ocular deviation.

Colobomata of the posterior segment with associated retinal detachment may be present without iris defect (30/50 had a coloboma of the posterior segment with normal irides). A large chorioretinal coloboma even with involvement of the optic disc may be consistent with moderately good central vision, but a superior visual field defect is to be expected. Refractive errors are common. Twelve of our patients have benefited from spectacles, and there may be ocular morbidity due to both meridional and strabismic amblyopia.

It is important for paediatricians to be aware of the ophthalmic features of the CHARGE association, since some, such as choroidoretinal coloboma, may be occult until complicated by retinal detachment. Ophthalmologists should be aware of the potential systemic associations of coloboma. Patients do not necessarily present as sick neonates to specialist centres; a few may be diagnosed later in life.

While the finding of typical colobomata is not specific to the CHARGE syndrome, additional findings such as facial nerve palsy may point to this diagnosis in a child with multiple abnormalities. We add a description of a dysplastic optic disc with marked peripapillary pigmentation. In addition two patients had atypical iris colobomata with normal fundi, while another had upper eyelid colobomata.

1 Pagon RA, Graham JM, Zonana J, Yong S-L. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981; 99: 223–7
2 Kaplan LC. Choanal atresia and its associated anomalies: Further support for the CHARGE association. *Int J Pediatr Otorhinolaryngol* 1985, 8: 237–42
3 Hittner HM, Hirsch NJ, Kreh GM, Rudolf AJ. Colobomatous microphthalmos, heart disease, hearing loss, and mental retardation – a syndrome. *J Pediatr Ophthalmol Strabismus* 1979; 16: 122–8.
4 Mitchell JA, Giangiacomo J, Hefner MA, Thelin JW, Pickens JM. Dominant CHARGE association. *Ophthalmic Paediatr Genet* 1985; 6: 31–6.
5 Metlay LA, Smythe PS, Miller ME. Familial CHARGE syndrome: clinical report with autopsy findings. *Am J Med Genet* 1987; 26: 577–81.
6 Oley CA, Baraitser M, Grant DB. A reappraisal of the CHARGE association. *J Med Genet* 1988, 25: 147–56
7 Warburg M. Ocular coloboma and multiple congenital anomalies: the CHARGE association. *Ophthalmic Paediatr Genet* 1983; 2: 189–99.
8 Stewart G, Young DG, Azmy AF. CHARGE association in neonates presenting with choanal atresia. *Z Kinderchir* 1987, 42: 12–3.
9 Brown OE, Burns DK, Smith TH, Rutledge JC. Bilateral posterior choanal atresia: a morphologic and histologic study, and computed tomographic correlation. *Int J Pediatr Otorhinolaryngol* 1987; 13: 125–42.
10 Rohn RD, Leffell MS, Leaden P, Johnson D, Rubio T, Emanuel BS. Familial third-fourth pharyngeal pouch syndrome with apparent autosomal dominant transmission. *J Pediatr* 1984, 105: 47–51.
11 Davenport SLH, Hefner MA, Mitchell JA. The spectrum of clinical features in CHARGE syndrome. *Clin Genet* 1986, 29: 298–310.
12 Hall BD. Choanal atresia and associated multiple anomalies. *J Pediatr* 1979, 95: 395–8.
13 Chestler RJ, France TD. Ocular findings in CHARGE syndrome. *Ophthalmology* 1988; 95: 1613–9
14 Bergstrom L. Syndromes associated with congenital facial paralysis. *Otolaryngol Head Neck Surg* 1981; 89: 336–42
15 Lin AE, Chin AJ, Devine W, Park SC, Zackai E. The pattern of cardiovascular malformation in the CHARGE association. *Am J Dis Child* 1987; 141: 1010–3.
16 Goldson E, Smith AC, Stewart JM. The CHARGE association: how well do they do? *Am J Dis Child* 1986, 140: 918–21.
17 Pardo JM, Chua C. The CHARGE association in a male newborn infant. *Clin Pediatr* 1985; 24: 531–3
18 Koletzko B, Majewski F. Congenital anomalies in patients with choanal atresia: CHARGE-association. *Eur J Pediatr* 1984; 142: 271–5
19 Leclerc JE, Fearon B. Choanal atresia and associated anomalies. *Int J Pediatr Otorhinolaryngol* 1987, 13: 265–72
20 Duncan NO, Miller RH, Catlin FI. Choanal atresia and associated anomalies: the CHARGE association. *Int J Pediatr Otorhinolaryngol* 1988, 15: 129–35
21 Cyran SE, Martinez R, Daniels S, St J Dignan P, Kaplan S. Spectrum of congenital heart disease in CHARGE association. *J Pediatr* 1987; 110: 576–8
22 August GP, Rosenbaum KN, Friendly D, Hung W. Hypopituitarism and the CHARGE association. *J Pediatr* 1983, 103: 424–5.
23 Curatolo P, Libutti G, Brinchi V. Infantile spasms and the CHARGE association. *Dev Med Child Neurol* 1983, 25: 367–73.
24 Ho CK, Kaufman RL, Podos SM. Ocular colobomata, cardiac defect, and other anomalies: a study of seven cases including two sibs. *J Med Genet* 1975; 12: 289–93.
25 Russell-Eggitt IM, Fielder AR, Levene MI, Young ID. Microphthalmos in a family. *Ophthalmic Paediatr Genet* 1985; 6: 121–8.
26 Fielder AR, Russell-Eggitt IM, Dodd KL, Mellor DH. Delayed visual maturation. *Trans Ophthalmol Soc UK* 1985, 104: 653–61
27 Flynn JT. In: Harley RD, ed. *Pediatric ophthalmology*. 2nd ed. Philadelphia: Saunders, 1983, 1: 13–4
28 François J. Colobomatous malformations. *Int Ophthalmol Clin* 1968, 8: 797–876
29 Mansour AM, Wang F, Henkind P, Goldberg R, Shprintzen R. Ocular findings in the facioauriculovertebral sequence (Goldenhar-Gorlin syndrome). *Am J Ophthalmol* 1985; 100: 555–9
30 Collins ET. Case with symmetrical congenital notches in the outer part of each lower lid and defective development of the malar bones. *Trans Ophthalmol Soc UK* 1900, 20: 190.

31 Lessick ML, Szego K, Wong PKW Trisomy 22 mosaicism with normal blood chromosomes *Clin Pediatr (Phila)* 1988; 27: 451–4.

32 Schinzel A, Schmid W, Fraccaro H, *et al* The 'cat eye syndrome': dicentric small marker chromosome probably derived from a no. 22 (tetrasomy 22pter –> q11) associated with a characteristic phenotype. *Hum Genet* 1981, 57: 148–58

33 Barakat AY, Butler MG. Renal and urinary tract abnormalities associated with chromosome aberrations *Int J Pediatr Nephrol* 1987, 8: 215–26

34 Tovo PA, Davi G, Fraceschini P, Delpiano A. Thymic hormone dependent immunodeficiency in an infant with partial trisomy of chromosome 22. *Thymus* 1986, 8: 313–8

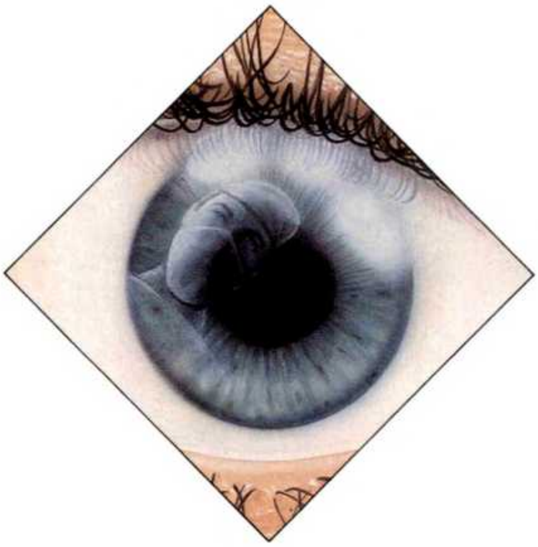
35 Boles DJ, Bodurtha J, Nance WE. Goldenhar complex in discordant monozygotic twins a case report and review of the literature. *Am J Med Genet* 1987; 28: 103–9

36 Evans JA, Reggin J, Greenberg C Tracheal agenesis and associated malformations· a comparison with tracheoesophageal fistula and the VACTERL association. *Am J Med Genet* 1985; 21: 21–34.

37 Weaver DD, Mapstone CL, Yu P-l The VATER association. *Am J Dis Child* 1986; 140: 224–9

38 Taylor A Autosomal trisomy syndromes A detailed study of 27 cases of Edwards syndrome and 27 cases of Patau's syndrome *J Med Genet* 1968, 5: 227.

39 Lillquist K, Warburg M, Andersen SR, Hagerstrand I. Coloboma of the iris, ciliary body and choroid in an infant with oesophago-tracheal fistula and congenital heart defects An unknown malformation complex *Acta Paediatr Scand* 1980; 69: 427–30



. . . WHEN YOU CHOOSE THE RIGHT SOLUTION

Alcon

BSS®

BALANCED SALT SOLUTION

With most ocular irrigation solutions corneal clouding can begin within a few minutes of commencing surgery. Whilst this clouding is usually reversible, it does make intraocular surgery such as cataract surgery more difficult because the detail within the eye is greatly obscured.[1]

BSS overcomes this problem. It has been designed to be similar to the physiological fluids that naturally bathe the eye. BSS therefore maintains a clear cornea and ensures that you can see the fine detail within the eye throughout surgery.[1,2]

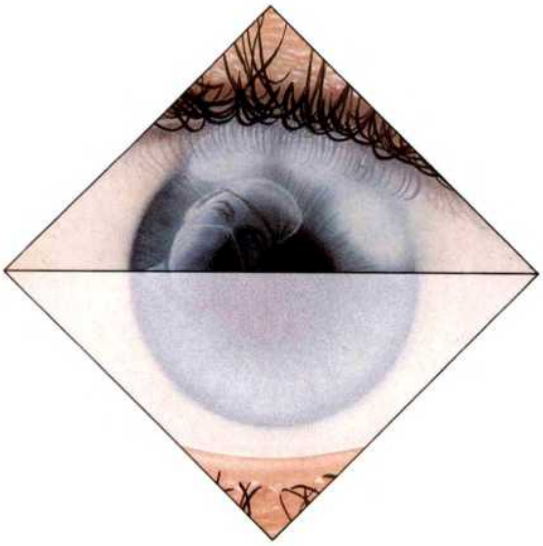
250ML AND 500ML BOTTLES

BSS is now available in a new 250ml size, specifically designed for the longer cataract procedures. One bottle will last through the whole operation and results in less wastage. BSS is now available in a full range of sizes ideal for all your surgical requirements.

So don't let the wrong solution cloud your vision.

Remember – only Alcon Balanced Salt Solution is – BSS.

® Registered Trademark.



THE DIFFERENCE IS CLEAR...

Prescribing Information.

Presentation: A sterile physiological balanced salt solution which is isotonic to the tissues of the eye. Containing Sodium Chloride Ph.Eur. 0.64%, Potassium Chloride Ph.Eur. 0.075%, Calcium Chloride Ph.Eur. 0.048%, Magnesium Chloride Hexahydrate Ph.Eur. 0.03%, Sodium Acetate Ph.Eur. 0.39%, Sodium Citrate Ph.Eur. 0.17% and Water for Injection Ph.Eur.

Uses: As a physiologic irrigating solution.

Dosage and Administration: Sufficient to produce the required irrigation.

Contra-indications, Warnings, etc:
There are no specific contra-indications for this product. When the corneal endothelium is abnormal, irrigation or any trauma may result in bullous keratopathy.
Not for intravenous infusion.
Contains no preservatives and should not be re-used.

Legal Category: P

Package Quantities: 15ml and 30ml Steri-Unit Drop-Tainer dispensers and 250ml and 500ml glass infusion bottles.

Product Licence Number: 15ml and 30ml Steri-Unit Drop-Tainer 0649/0007: 250ml and 500ml glass infusion bottles 0649/0099.

References

1. McDonnell PJ, Spalton DJ, Corneal clarity during extracapsular cataract surgery. Implant & Refractive Surgery, 1987; **6** (1): 9-13.
2. McDermott ML, et al, Ophthalmic Irrigants: A current review and update. Ophthalmic Surgery, 1988; **19** (10): 724-733.

Company Name and Address:

Alcon Laboratories (UK) Ltd,
Imperial Way, Watford,
Herts WD2 4YR.

Alcon

BSS®

BALANCED SALT SOLUTION

Electrophoretic assessment of aqueous and serum neurone-specific enolase in retinoblastoma and ocular malignant melanoma

B S F Shine, J Hungerford, B Vaghela, G A K Sheraidah

Abstract

The isoenzyme pattern of enolase was examined in the aqueous humour and serum of patients with retinoblastoma (10 aqueous, 8 sera), malignant melanoma (4 aqueous, 25 sera), and normal subjects undergoing cataract surgery (25 aqueous, 30 sera). The assay we used allowed assessment of all three major isoenzymes, including the $\gamma\gamma$ isoenzyme (neurone-specific enolase). No enolase was detectable in normal aqueous; $\alpha\alpha$ isoenzyme was present in the aqueous of one patient with malignant melanoma, while aqueous from all patients with retinoblastoma contained both $\alpha\alpha$ and $\gamma\gamma$. Normal serum contained only an $\alpha\alpha$ band, while serum from patients with retinoblastoma contained $\alpha\alpha$, $\alpha\gamma$, and $\gamma\gamma$ bands (7 sera, 87·5%), or $\alpha\alpha$ only (1 patient, 12·5%). All sera from patients with malignant melanoma contained the $\alpha\alpha$ band, with low levels of $\gamma\gamma$ in 16 (60%). In a single patient with Coats's disease $\alpha\alpha$ was present in the serum, but no enolase was detected in aqueous. Increased amounts of γ-containing isoenzymes of enolase are found in both serum and aqueous from patients with retinoblastoma. In malignant melanoma there is often an increase in serum $\gamma\gamma$ enolase. The assessment of aqueous and serum enolase patterns may be of value in the diagnosis of retinoblastoma and malignant melanoma.

The neurone-specific isoenzyme ($\gamma\gamma$) of enolase is demonstrable in tumours of neuroectodermal origin, such as retinoblastoma and neuroblastoma,[1 2] in aqueous humour from patients with retinoblastoma,[3] and in serum[4] and urine[5] from patients with neuroblastoma. Specific information about isoenzymes is yielded by measurement by radioimmunoassay,[6 7] enzyme immunoassay,[8 9] and electrophoretic separation,[10] but not by assays based on spectrophotometry[10 11] or luminescence.[12 13] Modification[14] of the electrophoretic assay, with a fluorescent endpoint, makes it more sensitive and rapid, allowing its application to small samples.

We wished to investigate the patterns of enolase isoenzymes in aqueous and serum from patients with malignant ocular tumours, and we describe here our clinical experience with electrophoretic assessment of this enzyme.

Patients, materials and methods

Aqueous humour samples were collected by paracentesis with a tuberculin syringe and disposable 25 gauge needle, with avoidance of blood contamination because of the high enolase activity in erythrocytes.[3] Samples were collected from enucleated eyes of patients with retinoblastoma and ocular malignant melanoma. A simultaneous serum specimen was drawn, care being taken to avoid haemolysis. Control aqueous samples were taken from patients undergoing cataract extraction at the time of entry into the anterior chamber. All samples were stored at −40°C until assay.

Adenosine diphosphate (ADP), adenosine monophosphate (AMP), nicotinamide adenine dinucleotide phosphate (NADP), 2-phosphoglycerate, hexokinase (EC 2.7.1.1), glucose-6-phosphate dehydrogenase (EC 1.1.1.49, from yeast), and pyruvate kinase (EC 2.7.1.40, from rabbit muscle) were obtained from Boehringer-Mannheim (Mannheim, FRG). Magnesium chloride hexahydrate, potassium chloride, and sucrose were obtained from Sigma Ltd, Poole, England. Cellulose acetate plates (ISO Flur Titan III) and electrophoretic buffer (Electra HR) were obtained from Helena Laboratories, Beaumont, Texas, USA. Electrophoresis tank and power pack (Vokam 2541) were obtained from Shandon Southern Products Ltd, Runcorn, Cheshire, England.

The visualisation reagent contained (per litre) trometamol (Tris) HCi (pH 7·4, 50 mmol), $MgCi_2$ (2 mmol), KCi (20 mmol), glucose (2 mmol), ADP (90 µmol), AMP (20 mmol), $NADP^+$ (0·5 mmol), phosphoglycerate (1·2 mmol), pyruvate kinase (4 KU), hexokinase (7 KU), and glucose-6-phosphate dehydrogenase (3·5 KU). To minimise diffusion, sucrose was dissolved in this reagent to give a final concentration of 300 g/l. Aliquots of 1 ml of the solution were stored at −20°C and thawed immediately before use.

For isoenzyme analysis, two cellulose acetate plates (76 by 60 mm) were soaked for 30 minutes in tris barbital sodium buffer (pH 8·6–9·0), removed, and blotted. To one (the sample plate), 1 µl of sample was applied near the cathodic end of the plate, and electrophoresis was carried out in tris barbital sodium buffer at 300 V for 7 minutes at room temperature. At the same time, the other (substrate) plate was placed membrane side up on a clean glass slide and 1 ml of isoenzyme reagent was poured on to the surface and allowed to soak for the period of electrophoresis. Following electrophoresis the sample plate was carefully placed on the substrate plate with the two wet surfaces apposed. The plates were compressed between prewarmed (37°C) glass plates and incubated at 37°C for 25 minutes. The plates were separated and dried at approxi-

Department of Pathology, Institute of Ophthalmology, London EC1
B S F Shine
B Vaghela
G A K Sheraidah

Moorfields Eye Hospital, London EC1
J Hungerford

Correspondence to.
Dr B Shine, Department of Pathology, Institute of Ophthalmology, 17–25 Cayton Street, London EC1V 9AT.

Accepted for publication 8 February 1990

TABLE I *Samples analysed for enolase isoenzymes*

Subjects	*Fluid*	*Number*
'Nomal'	Serum	30
	Aqueous	25
Malignant melanoma	Serum	25
	Aqueous	4
Retinoblastoma	Serum	8
	Aqueous	10
Coats's disease	Serum	1
	Aqueous	1

mately 57°C for 10 minutes. The fluorescence of NADPH thus produced was stable for at least 60 minutes at room temperature and for up to 1 month at −20°C. The fluorescent intensity of the bands was assessed visually with a UV lamp with maximum output at 365 nm. Plates were also scanned by means of a Perkin Elmer LS-5 fluorometer, with scanning attachment and output to a chart recorder (λ_{ex} 360 nm, λ_{em} 440 nm).

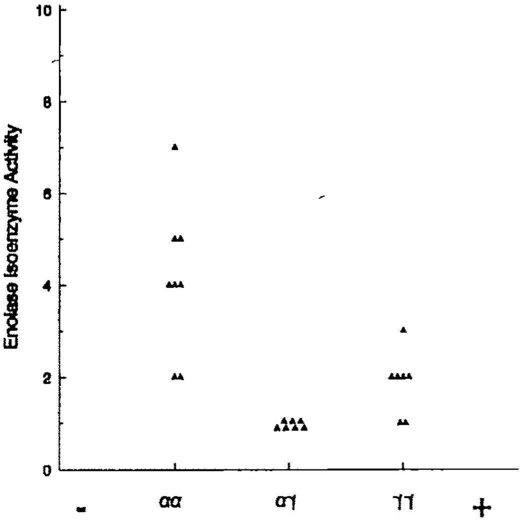


Figure 2: Levels of enolase isoenzymes in serum from patients with retinoblastoma.

Results

A maximum of three bands were detected by this procedure. The slowest band represents the αα isoenzyme, the intermediate band αγ isoenzyme, and the anodic band γγ isoenzyme.[14] Bands were visible only if 2-phosphoglycerate was included in the substrate medium, indicating that the enzyme was enolase. Visual assessment of the levels in each band appeared to correlate well with those obtained by scanning.

In total, 64 serum and 39 aqueous samples were examined (Table I). No enolase was detected in normal aqueous humour, and normal serum contained only the αα band with relative intensity ranging from 1+ to 2+. Aqueous humour from all eyes with retinoblastoma contained αα and γγ bands, with one sample also containing an intermediate (αγ) band (Fig 1). There was considerable variation in the relative intensities of the individual bands. Serum from all retinoblastoma patients contained an αα band, 7/8 (87·5%) also containing αγ and γγ bands (Fig 2).

An αα band was visible in aqueous humour from one patient of the four with malignant melanoma, but in none could αγ or γγ be demonstrated. The αα band was present in the serum of all 25 malignant melanoma patients, with relative intensities ranging from 1+ to 2+, and in 16 γγ (1+) was also present (Fig 3). In a single case of Coats's disease, an αα band was present in the serum with no enzyme visible in the aqueous.

Discusssion

Enolase (2-phospho-D-glycerate hydrolase, EC 4.2.1.11) is widely distributed in tissues, and reversibly catalyses the conversion of 2-phosphoglycerate to phosphoenol pyruvate. Its isoenzymes are dimers consisting of two subunits coded for by three gene loci (α, β, and γ[11]). In most adult tissues only the αα dimer is present, while in adult muscle and heart the ββ dimer predominates though αβ hybrids are demonstrable in the heart.[10] Since the γ subunit was previously believed to be expressed exclusively in mature neurones, γγ isoenzyme was designated neurone-specific enolase (NSE). However, low levels of NSE are present in some non-neuronal tissues.[15,16] The enzyme is not bound to cellular membranes and probably escapes freely following cell injury. γ-Subunits (that is, αγ and γγ[17]) containing enolase isoenzymes have been

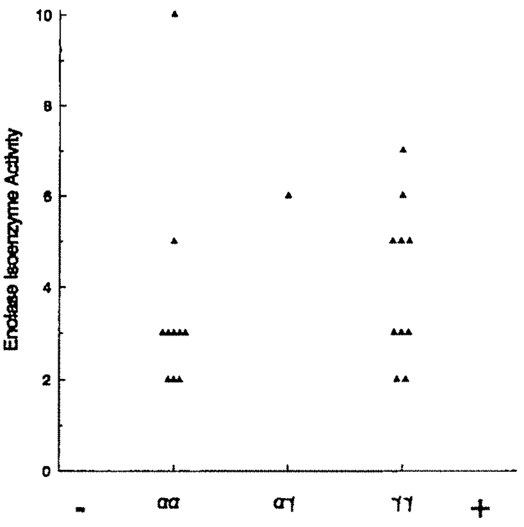


Figure 1: Levels of enolase isoenzymes in aqueous from patients with retinoblastoma.

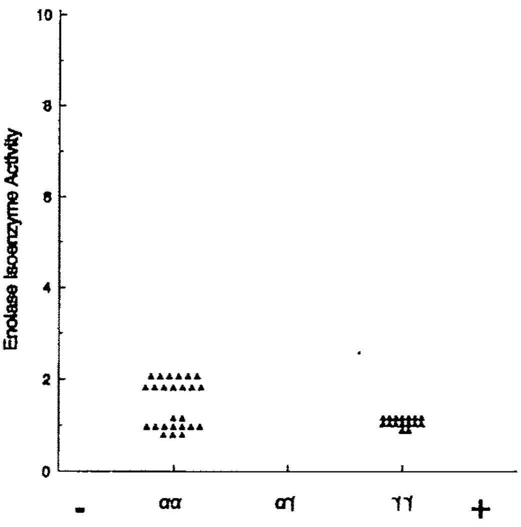


Figure 3: Levels of enolase isoenzymes in serum from patients with ocular malignant melanoma.

reported to be increased in the serum of patients with neuroblastoma,[4,18,19] medullary carcinoma of the thyroid,[20] and small-cell carcinoma of the lung,[21,22] in urine of patients with neuroblastoma,[5] and in the aqueous of patients with retinoblastoma.[3,19]

Methods for the measurement of enolase activity in tissues and biological fluids include spectrophotometric[10,11] and bioluminescence[12,13] assays for total enzyme, and radioimmunoassay[6,7] enzyme immunoassay,[8,9] immunohistochemistry,[1] and electrophoretic separation followed by colorimetric visualisation,[13] for measurement of isoenzymes. A modification of the eletrophoresis method[14] with fluorescence scanning makes it sensitive enough for use on small samples, with assessment of all isoenzymes within one hour.

Retinoblastoma is the commonest malignancy of infancy. It has features of both glial and neuroectodermal origin[1,2,23] and may be unilateral or bilalateral. With appropriate therapy in the early stages the prognosis is good.[24] Occasional spontaneous regression has been reported.[25] Correct diagnosis, without recourse to biopsy, is vital, since it is undesirable both to enucleate an eye for a benign condition and to miss a fatal, though potentially curable, malignant tumour. Rates of error worldwide, in the diagnosis of retinoblastoma have been estimated to be 25%.[26] If doubt about the diagnosis still exists after tests such as a CT scan have been performed, methods such as the assay of aqueous humour enzymes have been advocated.[27–29] However, although increased levels of serum and aqueous humour lactate dehydrogenase are often present in retinoblastoma, raised aqueous enzyme levels may be found in other conditions, such as Coats's disease.[30,31] Aqueous levels of γ–containing enolase isoenzyme have been shown by radioimmunoassay[3] to be raised in retinoblastoma. Paracentesis of the aqueous humour is sometimes necessary for the diagnosis of both primary[32,33] and secondary[34,35] anterior segment malignant tumours, though it is associated with a slightly increased risk of tumour dissemination.[36] In contrast, aspiration of vitreous, subretinal fluid, or tumour cyst material has been strongly discouraged.[32,33]

Using an electrophoretic assay[14] we have demonstrated different enolase isoenzyme patterns in aqueous humour and serum. Three bands were identified, corresponding to those previously reported to be αα, αγ and γγ isoenzymes. Aqueous from patients with retinoblastoma contains αα and γγ bands, while their serum often contains all three bands. The γ bands were absent from normal sera and normal aqueous but were faintly present as the γγ band in serum from two-thirds of patients with malignant melanoma. There were no differences between the sexes.

The presence of raised levels of NSE in serum and aqueous from patients with retinoblastoma is expected because of the presumed neuroectodermal origin of this tumour and its previous demonstration in tumour tissue.[1,2] Malignant melanoma arises from pigmented cells, in which NSE has been reported not to occur,[37] though Royds and colleagues[38] have identified the enzyme in malignant melanoma tissue. The existence of a faint γγ band in serum from patients with malignant melanoma may be due to leakage from the tumour, direct damage to the retina from raised intraocular pressure, or to metastatic spread.

Retinoblastoma is associated with increased levels of γγ-enolase in serum and aqueous. While serum levels may be of diagnostic help, there may be occasions when aqueous parcentesis is necessary for diagnosis. Because of the risk of tumour spread it should be reserved for cases where there is serious doubt about the diagnosis. The presence of a faint γγ band in serum from patients with malignant melanoma may also be of diagnostic value. However, further studies (both quantitative and qualitative) need to be performed on a larger population to assess the full potential of the assay.

1 Kivela T Neuron-specific enolase in retinoblastoma An immunochemical study *Acta Ophthalmol (KGL)* 1987, **64**: 19–25

2 Terenghi G, Polak JM, Ballesta J, *et al* Immunocytochemistry of neuronal and glial markers in retinoblastoma *Virchows Arch (A)* 1984; **404**: 61–73

3 Nakajima T, Kato K, Kaneko A, Tsumuraya M, Morinaga S, Shimosato Y High concentrations of enolase, alpha and gamma subunits, in the aqueous humour in cases of retinoblastoma *Am J Ophthalmol* 1986; **101**· 102–6

4 Zeltser PM, Marangos PJ, Evans AE, Schreider SL. Serum neuron-specific enolase in children with neuroblastoma Relationship to stage and disease course. *Cancer* 1986, 57: 1230–4

5 Goto Y-I, Hashimoto K, Tada K. Urine neuron-specific enolase and its clinical implication in patients with neuroblastoma *Tohoku J Exp Med* 1986; **149**. 67–72

6 Parma AM, Marangos PPJ, Goodwin FK A more sensitive radioimmunoassay for neuron-specific enolase suitable for cerebrospinal fluid determinations *J Neurochem* 1981; **36**: 1093–6.

7 Brown KW, Kynoch PAM, Thompson RJ Immunoreactive nervous system specific enolase (14-3-2 protein) in human serum and cerebrospinal fluid. *Clin Chim Acta* 1980, **101**: 256-64

8 Kato K, Suzuki F, Umeda Y Highly sensitive immunoassays for three forms of rat brain enolase *J Neurochem* 1981, 36. 793–7.

9 Kato K, Asai R, Schimizu A, Suzuki F, Ariyoshi Y. Immunoassay of three enolase isoenzymes in human serum and in blood cells. *Clin Chim Acta* 1983· **127**: 353-36

10 Rider CC, Taylor CB. Enolase isoenzymes in rat tissues Electrophoretic, chromatographic, immunological and kinetic properties *Biochim Biophys Acta* 1974; **365**: 285–300

11 Wold F *The enzymes* 3rd Ed New York and London: Academic Press, 1971, 5: 499–535.

12 Viallard JL, Murthy MRV, Dastugue B Ultramicro bioluminescence assay of enolase Application to human cerebrospinal fluid. *Neurochem Res* 1985, **10**: 1555-6

13 Wevers RA, Jacobs AAC, Hommes OR. A bioluminescence assay for enolase (EC4 2.1 11) activity in human serum and cerebrospinal fluid. *Clin Chim Acta* 1983; **135**: 159–68.

14 Viallard JF, Murthy MRV, Dastugue B Rapid electrophoretic determination of neuron-specific enolase isoenzymes in serum *Clin Chem* 1986; **32**: 593–6.

15 Hullin DA, Brown KB, Kynoch PAM, Smith C, Thompson RJ. Purification, radioimmunosassy and distribution of human brain 14-3-2 protein (nervous system specific enolase) in human tissues. *Biochim Biophys Acta* 1980, **628**· 98–108

16 Kato K, Ishigura Y, Suzuki F, Ito A, Semba R Distribution of nervous system-specific enolase isozymes in human serum and in blood cells *Clin Chim Acta* 1982, **127**: 353–63

17 Bock E, Dissing J Demonstration of enolase activity connected to the brain specific protein 14–3–2 *Scand J Immunol* 1975; **4**: 31–6

18 Ishiguro Y, Kato K, Shimizu A, Ito T, Magya M High levels of immunoreactive nervous system-specific enolase in sera of patients with neuroblastoma *Clin Chim Acta* 1982, **121**: 173–88

19 Beemer FA, Vlug AM, van Veelen CW, Rijksen G, Staal GEJ Isoenzyme pattern of enolase of childhood tumors *Cancer* 1984, **54**: 293–6

20 Oskam R, Rijksen G, Cees J, Lips M, Staal G E J Enolase isoenzymes in differentiated and undifferentiated medullary thyroid carcinomas. *Cancer* 1985, **55**: 934–9

21 Akoun GM, Scarna HM, Milleron BJ, Penichou MP, Herman DP. Serum neuron-specific enolase A marker for disease extent and response to therapy for small cell lung cancer *Chest* 1985, **87**: 39–43

22 Viallard JL, Caillard D, Kantelip B, Molina C, Dastugue B. Enzymatic determination of serum neuron-specific enolase in small cell lung cancers. *Chest* 1988, **93**: 1225–33.

23 Rodrigues MM, Wiggert B, Shields J, *et al* Retinoblastoma. Immunohistochemistry and cell differentiation. *Ophthalmology* 1987, **94**: 378–87
24 Albert DM Historic review of retinoblastoma. *Ophthalmology* 1987; **94**: 654–62
25 Abramson DH. Retinoma, retinocytoma, and the retinoblastoma gene *Arch Ophthalmol* 1983, **101**: 1517–8
26 Margo CE, Zimmerman LE. Retinoblastoma: the accuracy of clinical diagnosis in children treated by enucleation *J Pediatr Ophthalmol Strabismus* 1983, **20**: 227–9
27 Swartz M, Herbst RW, Goldberg MF. Aqueous humor lactic acid dehydrogenase in retinoblastoma. *Am J Ophthalmol* 1974; **78**: 612–7.
28 Das A, Roy IS, Maitra TK. Lactate dehydrogenase level and protein pattern in the aqueous humour of patients with retinoblastoma. *Can J Ophthalmol* 1983; **18**: 337–9
29 Dayal Y, Goyal JL, Jaffery NF, Agarwal HC Lactate dehydrogenase levels in aqueous humor and serum in retinoblastoma. *Jpn J Ophthalmol* 1985, **29**: 417–22
30 Jakobiec FA, Abramson D, Scher R. Increased aqueous lactate dehydrogenase in Coats' disease *Am J Ophthalmol* 1978; **85**: 686–9
31 Lifshitz T, Tessler Z, Maor E, Yassur Y Increased aqueous lactic dehydrogenase in Coats' disease *Ann Ophthalmol* 1987; **19**: 116–9.
32 Duke-Elder S *System of ophthalmology*. London: Kimpton, 1966; **9**: 900–2
33 Duke Elder S *System of ophthalmology* London. Kimpton, 1966; **10**: 710–2
34 Scholz R, Green WR, Baranano EC, Erozan YS, Montgomery BJ Metastatic carcinoma to the iris Diagnosis by aqueous paracentesis and response to irradiation and chemotherapy. *Ophthalmology* 1983, **90**: 1524–7
35 Woog JJ, Chess J, Albert DM, Dueker DK, Berson FG, Craft J. Metastatic carcinoma of the iris simulating iridocyclitis *Br J Ophthalmol* 1984, **68**: 167–73
36 Middleton WH Diagnosis of metastatic tumors of the anterior ocular segment *Am J Ophthalmol* 1952, **35**: 1329–34
37 Molnar ML, Stefansson K, Marton LS, Tripathi RS, Molnar GK. Immunohistochemistry of retinoblastoma in humans *Am J Ophthalmol* 1984; **97**: 301–7.
38 Royds JA, Rennie IG, Parsons MA, Timperley WR, Taylor CB. Enolase isoenzymes in uveal melanomas – a possible parameter of malignancy *Br J Ophthalmol* 1983; **67**: 244–8

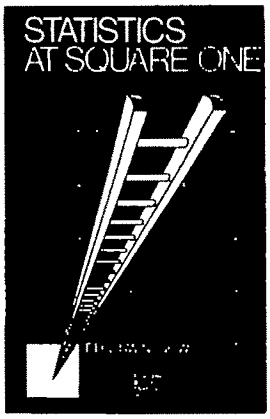
STATISTICS WITH CONFIDENCE
– Confidence intervals and statistical guidelines
MARTIN J GARDNER
DOUGLAS G ALTMAN
BMJ

Many medical journals, including the *British Medical Journal,* now expect scientific papers submitted to them to contain confidence intervals when appropriate. Why? what are they? and how do you calculate them? *Statistics with Confidence* tells you. A clear explanation of the reasons for using confidence intervals is followed by detailed presentation of methods of calculation, including numerous worked examples and specially compiled tables. To make things even easier, a computer programme, Confidence Interval Analysis (CIA), for calculating confidence intervals, has been specially designed by Martin Gardner and details are available from the Publishing Department, *British Medical Journal.*

Price: Inland £7.95;
Abroad £9.50
BMA members: Inland £7.45;
Abroad: £9.00

Eighth edition

The statistical testing of data is indispensable in many types of medical investigation and a help on countless occasions in clinical practice. This book provides step by step instruction. Subjects covered include standard deviation, χ^2 tests, t tests, non-parametric tests, and correlation. The book includes sections on Fisher's exact probability test and rank correlation not published in the original *BMJ* series. Methods specially adapted to pocket calculators.

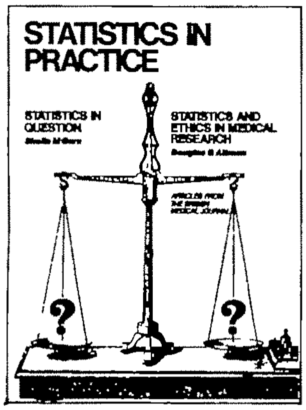


Price: Inland £3.00;
Abroad £4.50
BMA members: Inland £2.50;
Abroad: £4.00

"He uses statistics as a drunken man uses lamp-posts — for support rather than illumination." *

Let the *BMJ* throw light on your methods and help your results stand up

* *Andrew Lang*


STATISTICS IN
PRACTICE
STATISTICS IN QUESTION
STATISTICS AND ETHICS IN MEDICAL RESEARCH
ARTICLES FROM THE BRITISH MEDICAL JOURNAL

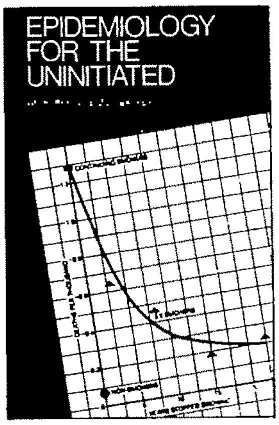
Fourth impression

No doctor can afford to ignore statistics: most modern medical research uses statistics. This important and authoritative book provides clear information on designing studies, applying statistical techniques, and interpreting studies that use statistics. It can be easily understood by those with no statistical training and should be read by all those who want to keep abreast of new developments.

Price: Inland £8.95;
Abroad £11.00
BMA members: Inland £7.45;
Abroad: £10.00

Second edition

Epidemiology has its own techniques of data collection and interpretation and its necessary jargon of technical terms, and in *Epidemiology for the Uninitiated* Professors Geoffrey Rose and David Barker guide the novice expertly through the theory and practical pitfalls. The second edition of this popular *BMJ* handbook has been revised to include further details of epidemiological methods and some of their more dramatic applications, such as the investigations on the Spanish cooking oil epidemic, and AIDS.



Price: Inland £3.95;
Abroad £5.50
BMA members: Inland £3.45;
Abroad: £5.00

ORDER FORM

BRITISH MEDICAL JOURNAL, P.O. Box 295,
London WC1H 9TE, England *or any leading medical bookseller*

Please send me
☐ Statistics with Confidence
☐ Statistics at Square One
☐ Statistics in Practice
☐ Epidemiology for the Uninitiated
All prices include postage, by air abroad

NAME ....

ADDRESS ....

....

POSTCODE ....

I enclose .... BMA Membership No. ....

Please make cheques payable to **British Medical Journal** o
debit my credit card (please tick box)

☐ Access/Mastercard ☐ Barclaycard/Visa
☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

CARD EXPIRY DATE ....

SIGNATURE ....

☐ Please send me a book catalogue

DID YOU TAKE YOUR DROPS?

What can you give a patien as well a

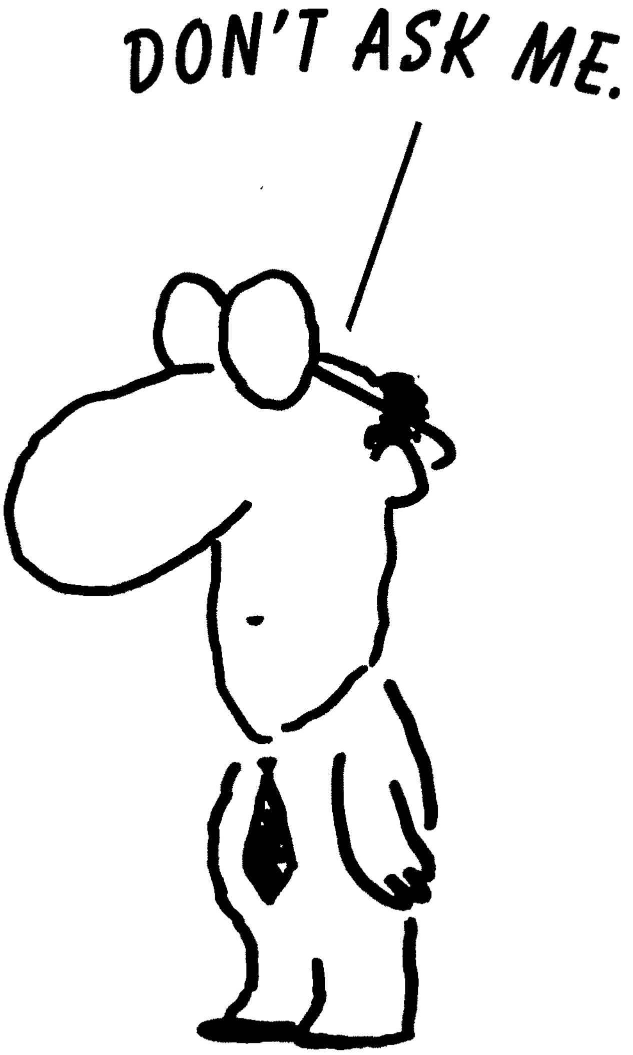
Getting patients to comply with complicated dose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, the beta blocker most patients only need to take once a day.

This is possible because of Betagan's sustained activity over 24 hours,[1] which has been shown to be effective in controlling the intr ocular pressure of up to 81% of patients on a once daily dose.[2]

Betagan offers new hope of improved cor pliance for a whole range of glaucoma patien such as the elderly or arthritic, those with impaired vision, or those who live alone.

▼ PRESCRIBING INFORMATION
PRESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v).
ACTION: Beta-adrenergic blocking agent.
INDICATIONS: Reduction of intraocular pressure in chronic open-angle glaucoma and ocular hypertension.
CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS: Contra-indications: Bronchial asthma; history of bronchial asthma; chronic obstructive pulmonary disease; sinus bradycardia; second and third deg atrioventricular block; cardiac failure; cardiogenic shock; hypersensitivity to a component. Caution in labile diabetes a in patients receiving oral beta-adrener



who suffers from amnesia glaucoma?

What's more you also have the option of rescribing Betagan at a twice daily dosage for ose patients who require additional control.

So next time you're looking for a simple ut flexible treatment for open angle glaucoma, onsider Betagan.

It's a name worth remembering.

NEW
BETAGAN®
(levobunolol hydrochloride 0.5%)
ONCE DAILY
ONE DROP THEY WON'T FORGET

---

cking agents. Do not use in patients ntinuing to wear hydrophilic (soft) ntact lenses. Transient ocular burning d stinging on instillation may occur. dycardia, hypotension, dyspnoea and hma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) once or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE:** £5.05 PL 0426/0060. Full prescribing information is available on request.

1. Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11.

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.
® Betagan is a registered trade mark.

An opportunity exists for

TWO SENIOR REGISTRARS WHO ARE FELLOWS OF THE COLLEGE OF OPHTHALMOLOGISTS

or its equivalent to serve as surgeons at

St. John Ophthalmic Hospital, Jerusalem

for a period of a year, a post recognised for accreditation in the United Kingdom.

The Hospital has 80 beds, with flats in the compound which can house a family. 50,000 patients mainly Moslems, attend each year and 5,000 major surgical procedures are performed. All modern equipment is at the disposal of the surgical staff. The outpatients department presents a high incidence of pathological and traumatic lesions.

The salary offered will be the same as is being earned by the successful candidate.

Fares each way for the surgeon and his family will be paid by the Order. The Hospital is housed in a compound which is safe for patients, staff and children.

Applications should be made to Sir Stephen Miller, KCVO, MD, FRCS, Hospitaller, The Order of St. John, 1 Grosvenor Crescent, London, SW1X 7EF.

BMJ BOOKS

For a complete Catalogue of BMJ Books

Please write to:
BRITISH MEDICAL JOURNAL,
P.O. Box 295,
London, WC1H 9TE

BMJ

ABC OF EYES

A R ELKINGTON P T KHAW

Detailed descriptions of the symptoms and signs of common disorders of the eye together with **over 120 colour illustrations** make the *ABC of Eyes* an invaluable aid to diagnosis.

Written by A R Elkington, senior lecturer and consultant ophthalmologist, University of Southampton, and P T Khaw, senior registrar in ophthalmology, Moorfields Eye Hospital, London, the book also provides guidance on when to refer to a specialist, and how urgently.

Busy general practitioners will find this a useful reference book for surgery while for medical students, optometrists, and nurses (particularly ophthalmic nurses) it offers a consise practical introduction to ophthalmology.

Chapters include:
History and examination • Red eye • Eyelid and lacrimal disorders • Injuries to the eye • Cataracts • Refractive errors • The glaucomas • Squint • The eye and the nervous system.

Inland £10.95; Abroad £12.50
BMA members:
Inland £9.95; Abroad £11.50
including postage by air abroad

Please enclose payment with order
***or* send us full details of your**
ACCESS, VISA or AMERICAN EXPRESS
credit card.

ORDER FROM British Medical Journal, PO Box 295, London WC1H 9TE *or any leading medical bookseller*

British Journal of Ophthalmology, 1990, 74, 431–432

MINI REVIEW

Ocular fluorophotophotometry

Recently there have been considerable developments in the techniques and potential uses of ocular fluorophotometry for the study of endogenous ocular fluorescence (the naturally autofluorescent compounds found in the retina, lens, or cornea) or the physiological barriers that protect the eye from its external environment. Corneal epithelial or endothelial cell function can be measured by topical application of fluorescein, a technique that has been used extensively in the contact lens and pharmaceutical industry, and this method can be adapted to measure the production of tears or aqueous humour and the function of the posterior capsule barrier. Measurement of the blood-aqueous barrier (BAB) or blood-retinal barrier (BRB) requires systemic administration of fluorescein either orally or intravenously.

Much of the stimulus to the study of the BRB by vitreous fluorophotometry came from the claim in the 1970s that a preretinopathy stage of diabetic retinopathy could be found when there was excessive retinal permeability to fluorescein in the absence of overt retinopathy. Further studies, however, failed to substantiate this claim, and to some extent vitreous fluorophotometry then fell into disrepute. Many of the initial problems arose from variability in equipment, techniques, and data processing, and the resolution of these problems has stimulated more interest. The development of the Fluorotron Master by Coherent Radiation has produced a fluorophotometer that is highly accurate, reliable, gives reproducible results, and can measure fluorescence in any part of the eye. This machine has stood the test of time and has been accepted as the 'gold standard'. More recently an EEC working party on ocular fluorophotometry has standardised protocols for each ocular barrier, providing European standards and common software. It will eventually provide a large pool of normal data, so that clinical studies will be directly comparable.

The clinical role of vitreous fluorophotometry has been re-established by work done in Chicago, Copenhagen, and at the Hammersmith Hospital in London. A single examination requires an hour with the patient, expensive equipment, and a skilled operator as well as an intravenous injection and at least two blood specimens, so its role is limited to clinical research. Vitreous fluorophotometry reflects permeability changes in the central 30° of the fundus[1] and can be performed only in the presence of an intact vitreous body, because a posterior vitreous detachment produces pooling and mixing artefacts which defy analysis. This is not, however, a tremendous practical problem, as a posterior vitreous detachment is easily identified by the fluorescent pattern in the gel, and these eyes excluded.

The Hammersmith group has shown that the degree of retinal permeability correlates with the severity of background diabetic retinopathy, and, particularly in the macular area, it provides a useful objective index of the extent of diabetic background retinopathy.[2] It thus confirms earlier results from Chicago which showed a good correlation between BRB permeability, visual acuity, and the extent of retinal thickening in diabetic macular oedema.[3] This has become particularly relevant with the advent of clinical trials of various aldose reductase inhibitors in diabetic retinopathy. Studies in Copenhagen have shown that antihypertensive treatment lowers increased BRB permeability in diabetic eyes and that lowering of the blood pressure within the normal range with captopril tends to stabilise the BRB in diabetic patients, whereas the BRB of untreated patients tends to deteriorate.[4]

These observations provide an insight into how the deleterious effects of systemic hypertension are mediated in diabetic retinopathy. Abnormal permeability of the BRB can be found in a wide variety of ocular diseases, but its measurement is not worthwhile unless it is part of the primary disease process or provides a means to study disease progression or treatment. It does, for instance, provide an excellent method of quantifying recovery of the BRB after central retinal vein occlusion.[5] Quantification of damage to the blood-aqueous barrier has wide implications in anterior segment surgery and inflammatory eye disease. The BAB is much more permeable than the BRB, and different problems are encountered in its measurement. In normal eyes the blood vessels contributing to the barrier appear to be about 10 times more permeable to fluorescein than those of the BRB.[6] Intravenous fluorescein is rapidly bound to albumin in the plasma and also metabolised to fluorescein glucuronide, so that one hour later only about 17% of the dose is still present as free fluorescein. These metabolites have less fluorescence than free fluorescein (30% and 5% respectively) and are more water soluble, so that the kinetics of their inward and outward transport across the BAB are different from those of free fluorescein. In the normal eye most of the fluorescence in the aqueous humour after intravenous fluorescein is due to free fluorescein, principally leaking from the iris vessels, but in the pathological eye this is no longer the case, as significant contributions can be made through the ciliary body and by the other metabolites. For this reason elegant equations to explain the BAB in the normal eye cannot be applied, and the BAB has been variously measured as a permeability or diffusion coefficient of varying complexity, the ratio of fluorescence between a normal and abnormal eye, a peak level of fluorescence, or a percentage change from a previous value. The recent EEC working party has chosen a diffusion coefficient to standardise on.

Fluorophotometry for measurement of the BAB may well, though, be soon superseded by laser devices which measure the light scattering effect of cells and protein in the anterior chamber. Kowa have produced a commercial machine which scans a small volume of the anterior chamber with a He-Ne laser and measures reflected light from material within the anterior chamber by a sensitive photomultiplier. Mathematical analysis of the reflected photons distinguishes protein concentration from the cell count. The technique has the enormous advantages of being entirely non-invasive and extremely rapid and easy to perform, and initial work with the equipment seems to support the high expectations held for it and the expense.[7,8]

Lens autofluorescence has been a neglected area of study. There has been speculation that it might provide a long term index of diabetic control reflecting blood sugar changes over years which, if substantiated, would be of great relevance to the prediction of diabetic complications.

New developments in fluorophotometry require better instruments with increased resolution to distinguish inner and outer BRB function and differential spectroscopy to separate the spectrum of fluorescein from fluorescein glucuronide, which would provide another molecule with different pharmokinetics with which to study the BRB. Further developments in ocular spectroscopy have a ring of science fiction about them, but the technology is rapidly becoming available – for instance, to measure melanin and lipofuscin concentrations in the retina by time resolved spectroscopy, in which the molecule is stimulated by monochromatic light, and the time delay of the resultant fluorescence is analysed in pico or nano seconds. It is not beyond the realms of possibility to suggest it will be possible to perform in vivo immunofluorescence or fluorocytometry on the aqueous humour.

D J SPALTON

Medical Eye Unit,
St Thomas's Hospital
London SE1 7EH

1 Dalgaard P, Barker VA, Lund-Anderson H. Vitreous fluorophotometry – mathematical analysis of the effect of peripheral leakage on axial scans. *Invest Ophthalmol Vis Sci* 1989; 30: 1522–6
2 Plehwe WE, Sleightholm MA, Kohner EM Does vitreous fluorophotometry reflect the severity of diabetic retinopathy? *Br J Ophthalmol* 1989; 73: 255–60.
3 Smith RT, Lee CM, Charles HC, *et al* Quantification of diabetic macular oedema *Arch Ophthalmol* 1987; 105: 218–22.
4 Parving HH, Larsen M, Hommel E, Lund-Anderson H. Effect of antihypertensive treatment on blood retinal barrier permeability to fluorescein in hypertensive type I (insulin dependent) diabetic patients with background retinopathy. *Diabetologica* 1989; 32: 440–4.
5 Chalal PS, Fallon TJ, Kohner EM. Measurement of blood retinal barrier function in central retinal vein occlusion *Arch Ophthalmol* 1986; 104: 554–7.
6 van Best JA, Lappelhof JP, Laterveer L, Ooster-huis JA. Blood aqueous barrier permeability vs age by fluorophotometry. *Curr Eye Res* 1987; 6: 855–63.
7 Sawa M, Tsurumaki Y, Tsuru T, Shimizu H New quantitative method to determine protein concentration and cell number in the aqueous in vivo. *Jpn J Ophthalmol* 1988; 32: 132–42
8 Shah SM, Spalton DJ, Smith SE. Factors affecting the interpretation of results from the Kowa FC 1000 Laser Cell Flare Meter in normal eyes (In press).

CASE REPORTS

Endogenous *Nocardia asteroides* endophthalmitis in a patient with systemic lupus erythematosus

Y Ishibashi, R Watanabe, S Hommura, A Koyama, T Ishikawa, Y Mikami

Institute of Clinical Medicine, University of Tsukuba, Tsukuba
Department of Ophthalmology
Y Ishibashi
R Watanabe
S Hommura

Department of Internal Medicine
A Koyama
T Ishikawa

Research Centre for Pathogenic Fungi and Microbial Toxicoses, Chiba University, Chiba, Japan
Y Mikami

Correspondence to:
Dr Y Ishibashi,
Department of Ophthalmology, Institute of Clinical Medicine,
University of Tsukuba,
Tsukuba-shi, Ibaraki, 305
Japan.

Accepted for publication
2 February 1990

Abstract

We report a case of endogenous *Nocardia* endophthalmitis in a patient with systemic lupus erythematosus (SLE). He developed a parafoveal lesion in the right fundus while on systemic corticosteroid and antibiotic treatment. Initially we suspected a fungal origin and treated him with antifungal drugs. The intraocular disease progressed without improvement and advanced to the vitreous cavity. *Nocardia asteroides* was found in a specimen obtained at pars plana vitrectomy and was also cultured from the same specimen. The intraocular infection was controlled by antibacterial drugs, though the visual acuity of the right eye was reduced to only light perception owing to heavy vitreous opacity and secondary cataract. This case is the first report of endogenous *Nocardia* endophthalmitis in Japan and also the first case of this disease reported from outside the United States of America.

Nocardia asteroides is a Gram-positive, weakly acid-fast, filamentous, aerobic organism which is generally considered to be a bacterium despite certain morphological and staining properties in common with fungi.[1] The clinical features of nocardial infection closely resemble those of fungal infections, though *Nocardia* has no sensitivity to antifungal agents. It is evident from some studies that nocardiosis is a disease of much greater frequency than was formerly recognised.[2,3] Lung, skin and subcutaneous tissue, brain, and pleura are common sites of the infection. Haematogenous dissemination, usually from a primary pulmonary focus, has been estimated to occur in approximately one-third of the cases. Intraocular infection, a rare site, has been reported in 14 patients,[4-14] typically leading to enucleation or death. Endogenous ocular dissemination has been found in patients with renal transplants,[7,8] lymphocytic lymphoma,[9] hypogammaglobulinaemia.[10] Hodgkin's disease,[11] lupus erythematosus,[12] diabetes mellitus,[13] and systemic sclerosis.[14] We observed endogenous *Nocardia* endophthalmitis in a patient with systemic lupus erythematosus (SLE).

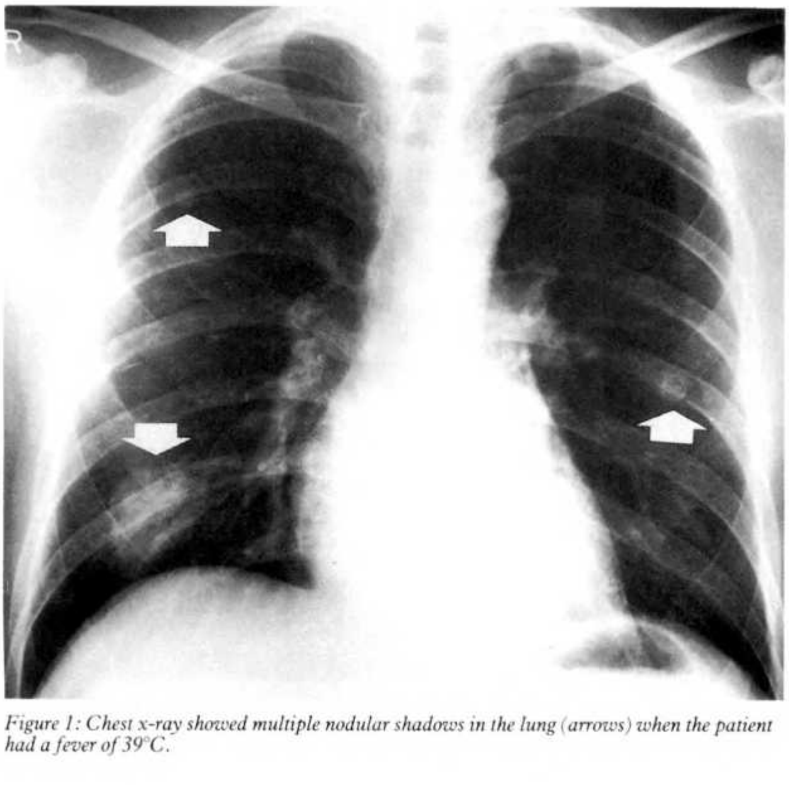


Figure 1: Chest x-ray showed multiple nodular shadows in the lung (arrows) when the patient had a fever of 39°C.

Case report

The subject was a 27-year-old man who had a history of admission to hospital with systemic eruption, fever, nasal bleeding, and photosensitivity. He was diagnosed as having systemic lupus erythematosus by a biopsy of the kidney when he was 14 years old. He was also admitted to hospital at 16 years old, 19 years old, and 24 years old with various symptoms considered to be unrelated to the systemic lupus erythematosus. The histopathological diagnosis by biopsy of the kidney was diffuse mesangial proliferation with adhesions, at his last admission to hospital. He took oral corticosteroid (prednisolone 10 mg/day) as an outpatient but stopped suddenly without consulting his doctor.

The patient developed systemic oedema and ascites, symptoms of nephrotic syndrome, at the beginning of March 1987, and entered the University Hospital of Tsukuba on 15 May, 1987. His condition was controlled with 60 mg of oral prednisolone. He had a fever of 39°C on 1 August. Multiple nodular shadows in the lungs were found on *x*-ray (Fig 1), and cavity formation was disclosed by roentogeno-tomography. The fever was reduced to 37°C by administration of antibiotics, but the patient complained of blurred vision in his right eye on 19 August. He

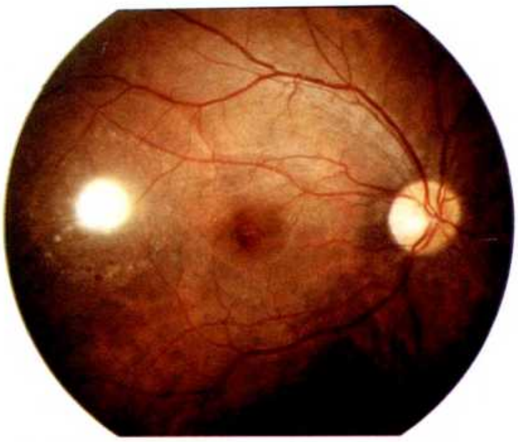


Figure 2: Right ocular fundus of the patient at initial examination. Temporal to the macula is an exudative lesion with thin retinal detachment.

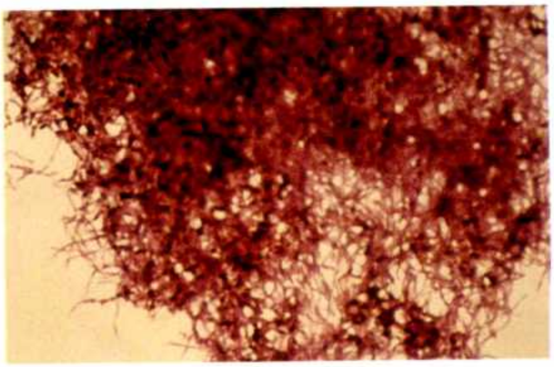


Figure 4: Gram-positive, filamentous organisms were found in the specimen obtained from a pars plana vitrectomy. (Gram stain, original magnification, × 100).

was referred to the Department of Ophthalmology on 27 August 1987.

The visual acuity of his right eye was 20/25, and a slit-lamp examination disclosed a mildly inflamed conjunctiva. There was a moderate inflammatory reaction in the anterior chamber and vitreous body. No changes were recognised in the cornea or the lens. Ophthalmoscopic examination of the right eye disclosed a paramacular exudative lesion located temporally of the macula. The lesion was round, whitish yellow, 1 mm in diameter, slightly elevated towards the vitreous cavity, with a thin retinal detachment (Fig 2). In the left eye there were mild inflammatory cells in the anterior chamber and vitreous body, but no changes were found in the cornea, lens, or fundus.

We suspected initially fungal infection from his history and clinical features; moreover a *Candida* sp. was found in a culture of sputum. Itraconazole, 150 mg/day by mouth, a new triazole antifungal agent, was started for the ocular infection. Despite this treatment the retinal lesion developed gradually (Fig 3). Intravenous miconazole 1200 mg/day, was added to the therapy on 6 September, but the infection progressed without improvement. Pars plana vitrectomy with miconazole infusion (100 mg/l) was performed on 18 September, 1987. Gram-positive, filamentous organisms (Fig 4) were found in the specimen obtained at vitrectomy, and many orange colonies grew on heart infusion agar. This organism was determined as *Nocardia asteroides* by morphological features on Sabouraud agar and brain heart infusion agar (Fig 5), by microscopic features on a slide culture, and by biochemical and physiological studies such as analysis of cell wall compositions, ability to hydrolyse adenine, caseine, hypoxanthine, tyrosine, urea, or xanthine, and utilisation of acid production from various carbon sources.

Immediately after the diagnosis of nocardiosis on 22 September, 1987 the treatment was changed to oral trimethoprim (1600 mg) and sulfamethoxazole (320 mg) per day, but the ocular infection did not improve. On 30 September, in line with the results of a sensitivity test (Table I), intravenous cefotaxime (2 g/day), oral minocycline (200 mg/day), and intramuscular amikacin (100 mg/day) were started instead of trimethoprim and sulphamethoxazole. The ocular infection reacted gradually to this therapy. On 13 October, the doses of these drugs were reduced to 1 g of cefotaxime, 100 mg of minocycline, and 50 mg of amikacin. During this time intraocular and pulmonary infections were well controlled by the therapy.

After one month of treatment the infection had subsided, though the right ocular fundus was not observable, and visual acuity was reduced to only light perception because of secondary cataract and heavy vitreous opacity. There were no signs of chronic inflammation in his right eye, and B-scan ultrasonography

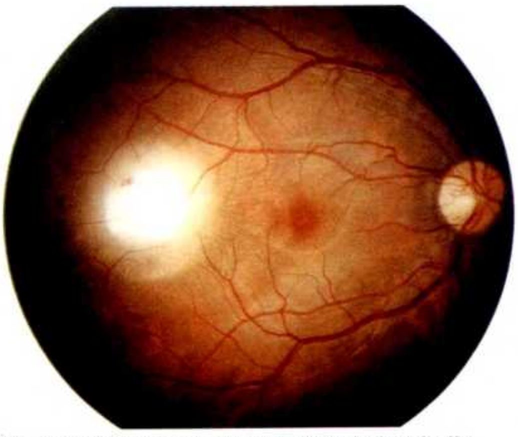


Figure 3: One week later the ocular lesion had gradually progressed in spite of taking oral itraconazole.

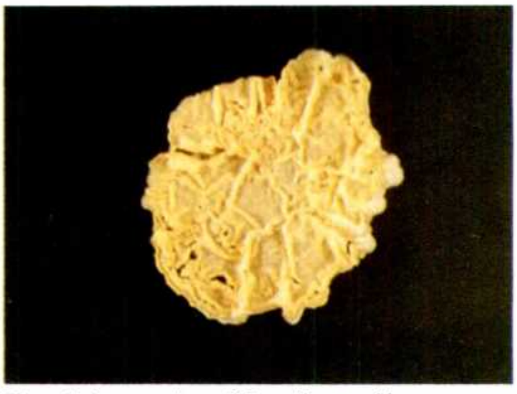


Figure 5: A macrocolony of Nocardia asteroides *on brain-heart infusion agar (Difco) for three weeks at 27°C. The size of colony was 20 to 35 mm in diameter.*

TABLE I *In vitro susceptibility of this strain of Nocardia asteroides to various antimicrobial agents*

Agent	*MIC value (mg/l)**
Ampicillin	100 00
Amikacin	0 78
Cefotaxime	3 12
Gentamicin	50·0
Doxycycline	1·5
Minocycline	0·39
TMP-SMX†	25 0
SMX	100·0

*Minimum inhibitory concentration (MIC) was defined as the lowest concentration suppressing all growth during seven days of incubation at 27°C Sensitivity disc agar (Nissui, Japan) was used
†TMP=Trimethoprim SMX=sulfamethoxazole, combination in fixed-weight ratio (1 5)

showed no retinal detachment at the end of therapy. Moreover, the left eye had no inflammation in the anterior chamber or the vitreous, and the visual acuity remained at 20/20. The pulmonary infection also reacted to the systemic treatment, and the patient was discharged on 18 November, 1987.

Discussion

Endogenous *Nocardia* endophthalmitis is disseminated from the primary site of infection, mainly from pulmonary lesions, and has been reported in only 14 patients (Table II). All were from the United States. In 1961 Murray and associates[3] stated that no documented cases had been found in the oriental literature. Although nocardiosis has been recognised throughout the rest of the world, most reports on it have originated from the United States and Europe. This case is the first report of endogenous *Nocardia* endophthalmitis in Japan and also the first case from outside of the United States. All reported cases of endogenous endophthalmitis were caused by *Nocardia asteroides* except for one case which was not determined in detail.[7] Our case was also caused by *N asteroides*. Beaman and associates[2] reported that *N asteroides* accounted for 86% of infections clinically limited to the lung, 92% of central nervous system infections, and 73% of systemic infections.

Delays in the early diagnosis and treatment of nocardiosis are often due to confusion with pulmonary tuberculosis, systemic mycoses, and the closely related actinomycosis.[2] We initially confused the infection with one of fungal origin because of similarity of clinical features, the patient's past history, and cultivation of a *Candida* sp. from the sputum. *Candida* sp, are sometimes cultured from the throat, intestinal duct, or sputum as clinically saprophytes. The correct diagnosis is imperative, because nocardiosis is refractory to antifungal agents. After pars plana vitrectomy *N asteroides* was found to be the causative agent of the intraocular and pulmonary infections.

The distribution of nocardiosis by sex shows that men outnumber women by about 3:1,[2] though for endogenous intraocular infections men outnumbered women by about 7:1. Most patients have been between the ages of 21 and 50, though the age range for *Nocardia* infections in the United States is broader.[2] The 15 patients with endogenous *Nocardia* endophthalmitis were between the ages of 15 and 77 (average 46·2) years.

Presant and associates[15] suggested that patients who had received corticosteroids or immunosuppressive therapy had a significantly higher mortality rate from localised nocardiosis than previously healthy persons or patients with serious underlying conditions but who were not receiving corticosteroids or immunosuppressive drugs. Ophthalmologists should consider endogenous *Nocardia* endophthalmitis as well as intraocular mycosis or tuberculosis when patients have metastatic infectious lesions in their ocular fundi while on corticosteroids or are on immunosuppressive therapy.

In this case the diagnosis was confirmed by examination of a specimen obtained from a pars plana vitrectomy. The diagnostic value of the vitrectomy was excellent, though the therapeutic effect was not clear. Sher *et al*[10] reported a case of bilateral intraocular *Nocardia* infection, in which the condition in the left eye partially resolved after pars plana vitrectomy whereas the right eye, which had not undergone vitrectomy, had active ocular infection at the patient's death. In their case the diagnosis was established before the vitrectomy, and the patient was treated with several drugs for nocardiosis. They found filamentous beaded organisms resembling *Nocardia* in a specimen removed at surgery, though cultures of this material, inoculated on to several media, showed no growth after four weeks of incubation. We considered that *Nocardia* was not alive in their case at the time of the vitrectomy. On the other hand *Nocardia* was confirmed by both direct examination and cultures of the vitreous specimen in our case, and

TABLE II *Summary of reported cases*

Study	*Patient*	*Organism*	*Steroid*	*Immunosuppressive drug*	*Previous disease*
Davidson and Foerster[4]	46, M	*N asteroides*	Yes	No	Gall bladder disease
Meyer *et al*[5]	67, M	*N asteroides*	No	No	Gunshot wound
Meyer *et al*[5]	56, M	*N asteroides*	?	?	?
Burpee and Starke[6]	20, M	*N asteroides*	No	No	Leg wound
Panijayanond *et al*[7]	50, M	*N asteroides*	Yes	Yes	Renal transplant
Jampol *et al*[8]	40, M	*N asteroides*	Yes	Yes	Wegener's granuloma, renal transplant
Rogers and Johnson[9]	77, F	*Nocardia* sp.	Yes	Yes	Malignant lymphoma
Sher *et al*[10]	38, M	*N asteroides*	Yes	No	Hypogammaglobulinaemia
Lissner *et al*[11]	60, M	*N asteroides*	Yes	No	Hodgkin's disease
Smith *et al*[12]	23, M	*N asteroides*	Yes	Yes	Lupus erythematosus, renal transplant
Bullock[13]	15, M	*N asteroides*	Yes	Yes	Paroxysmal nocturnal haemoglobinuria
Bullock[13]	59, M	*N asteroides*	No	No	Diabetes mellitus
Ferry *et al*[14]	66, M	*N asteroides*	No	No	?
Ferry *et al*[14]	49, F	*N asteroides*	Yes	No	Scleroderma
Ishibashi *et al*	27, M	*N asteroides*	Yes	No	Systemic lupus erythematosus

M=male. F=female

adequate treatment was not performed at surgery, because the diagnosis was not definite. To determine the value of vitrectomy in the treatment of intraocular *Nocardia* infection we need more clinical experience and experimental study.

1 Dubos RJ, Hirsch JG *Bacterial and mycotic infections of man* 4th ed Philadelphia. Lippincott, 1965.

2 Beaman BL, Burnside J, Edwards B, Causey W *Nocardia* infections in the United States 1972–1974 *J Infect Dis* 1976; 134: 286–9

3 Murray JF, Finegold SM, Froman S, Will DW The changing spectrum of nocardiosis. A review and presentation of nine cases. *Am Rev Respir Dis* 1961, 83: 315–30.

4 Davidson S, Foerster HC. Intraocular nocardial abscess endogenous. *Ophthalmology* 1967; 71: 847–50

5 Meyer SL, Font RL, Shaver RP Intraocular nocardiosis Report of three cases *Arch Ophthalmol* 1970; 83: 536–41

6 Burpee JC, Starke WR. Bilateral metastatic intraocular nocardiosis. *Arch Ophthalmol* 1971; 86: 666–9.

7 Panijayanond P, Olsson CA, Spivack ML, *et al* Intraocular nocardiosis in a renal transplant patient *Arch Surg* 1972, 194: 845–7

8 Jumpol LM, Strauch BS, Albert DM Intraocular nocardiosis *Am J Ophthalmol* 1973, 76: 568–73.

9 Rogers SJ, Johnson BL. Endogenous *Nocardia* endophthalmitis, Report of a case in a patient treated for lymphocytic lymphoma *Ann Ophthalmol* 1977; 9. 1123–31

10 Sher NA, Hill CW, Eifrig DE Bilateral intraocular *Nocardia asteroides* infection. *Arch Ophthalmol* 1977, 95: 1415–8.

11 Lissner GS, O'Grady R, Choromokos E. Endogenous intraocular *Nocardia asteroides* in Hodgkin's disease. *Am J Ophthalmol* 1978; 86: 388–94

12 Smith PW, Steinkraus GE, Henricks BW, Madson EC CNS nocardiosis. *Arch Surg* 1980, 37: 729–30

13 Bullock JD. Endogenous ocular nocardiosis a clinical and experimental study *Trans Am Ophthalmol Soc* 1983, 81: 451–531

14 Ferry AP, Font RL, Weinberg RS, Boniuk M, Schffer CL Nocardial endophthalmitis report of two cases studied histopathologically *Br J Ophthalmol* 1988, 72· 55–61

15 Presant CA, Wiernik PH, Serpick AA. Factors affecting survival in nocardiosis *Am Rev Respir Dis* 1973, 108: 1444–8

OPHTHALMOLOGY

Pediatric Ophthalmology

Edited by D S I Taylor

This is a major reference text giving definitive, comprehensive coverage of paediatric ophthalmology. The text is condensed yet exhaustive and covers both the common and the rare. There are contributions from some of the world's leading ophthalmologists. The book is divided into six major parts: Growth and Development, The Clinical Approach, Allergy and Infection, Problems of Anatomical Origin, Systemic and Neurological Issues, Eye Movements and Strabismus. In each part there are sections describing major clinical problems along with the more classical disease orientated approach eg. failure to thrive, the odd looking eye, the deaf-blind child, wobbly eyes. The book embraces the concerns of the 'whole child', not just paediatric ophthalmology.

- covers all aspects of paediatric ophthalmology • edited by a leading ophthalmologist
- over 600 illustrations, many in full colour, throughout the text
- accent on detail and referencing • international authorship • 22 sections of practical problems

May 1990. 736 pages, 660 illustrations. ***£135.00*** *0 86542 117 X*

ALSO AVAILABLE

Greer's Ocular Pathology *Fourth Edition*

D R Lucas

Dr Lucas had produced a comprehensively revised and expanded edition of Greer's Ocular Pathology, presented in an attractive two column format. Like the original, the revised edition provides a concise account of the pathology of eye disease to complement the clinical ophthalmological texts used in training. New chapters have been included on the optic nerve, the phacomatoses, lymphoid hyperplasias and lymphomas, and congenital anomalies.

1989. 352 pages, 222 illustrations.
£67.50 *0 632 01513 6*

Clinical Anatomy of the Eye

R S Snell & M A Lemp

This book is written to provide the ophthalmologist and the optometrist with the basic knowledge of clinical anatomy necessary to practise ophthalmology. The practical application of anatomical facts to ophthalmology has been emphasized throughout the book in the form of clinical notes in each chapter. Clinical problems requiring anatomical knowledge for their solution are presented at the end of each chapter.

"... the book is a useful, delightful, much needed contribution." ***Contact Lens Journal***

1989. 376 pages, 195 illustrations.
Hardback ***£69.50*** *0 86542 053 X*
Paperback ***£29.50*** *0 86542 086 6*

FORTHCOMING TITLE

The Pathogenesis and Management of Graves' Ophthalmopathy

Contemporary Issues in Endocrinology and Metabolism: Volume 1

Edited by J R Wall and J How

- covers every aspect of diagnosis and treatment of Graves' Ophthalmopathy
- contains contributions from an international group of experts
- covers immunology and the eye and describes the association between the eye and autoimmune eye disorders
- contains extensive coverage of clinical manifestations of the disease and clinical techniques and tests
- covers medical management and treatment including new drugs and corrective eye surgery

Late 1990. 208 pages, 58 illustrations. ***£45.00 (approx)*** *0 86542 112 9*

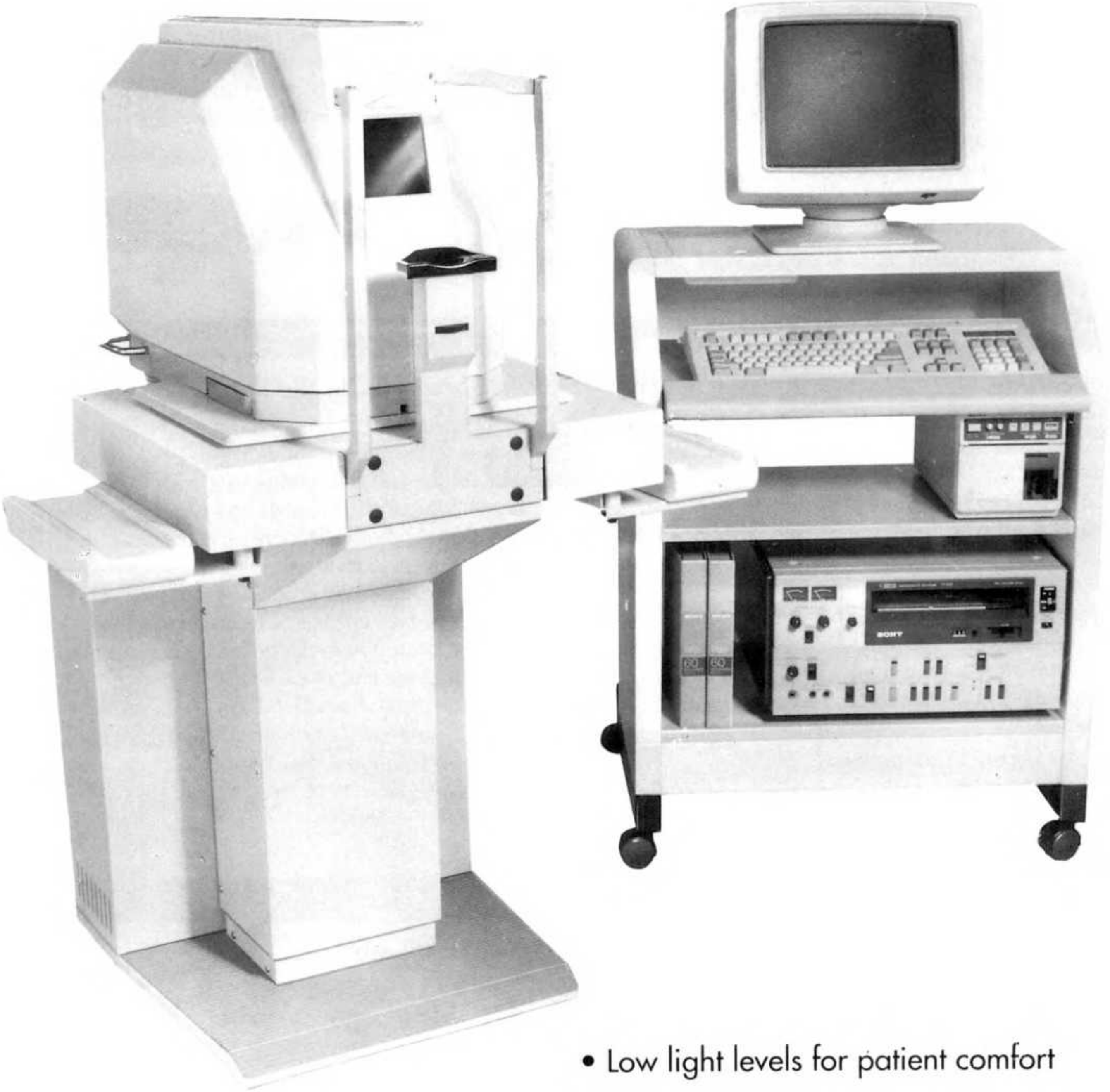
For further information contact the Medical Marketing Department at the address below.

BSP

BLACKWELL SCIENTIFIC PUBLICATIONS LTD
Osney Mead, Oxford OX2 0EL, UK Tel: (0865) 240201

AT CLEMENT CLARKE WE ONLY EXPEC

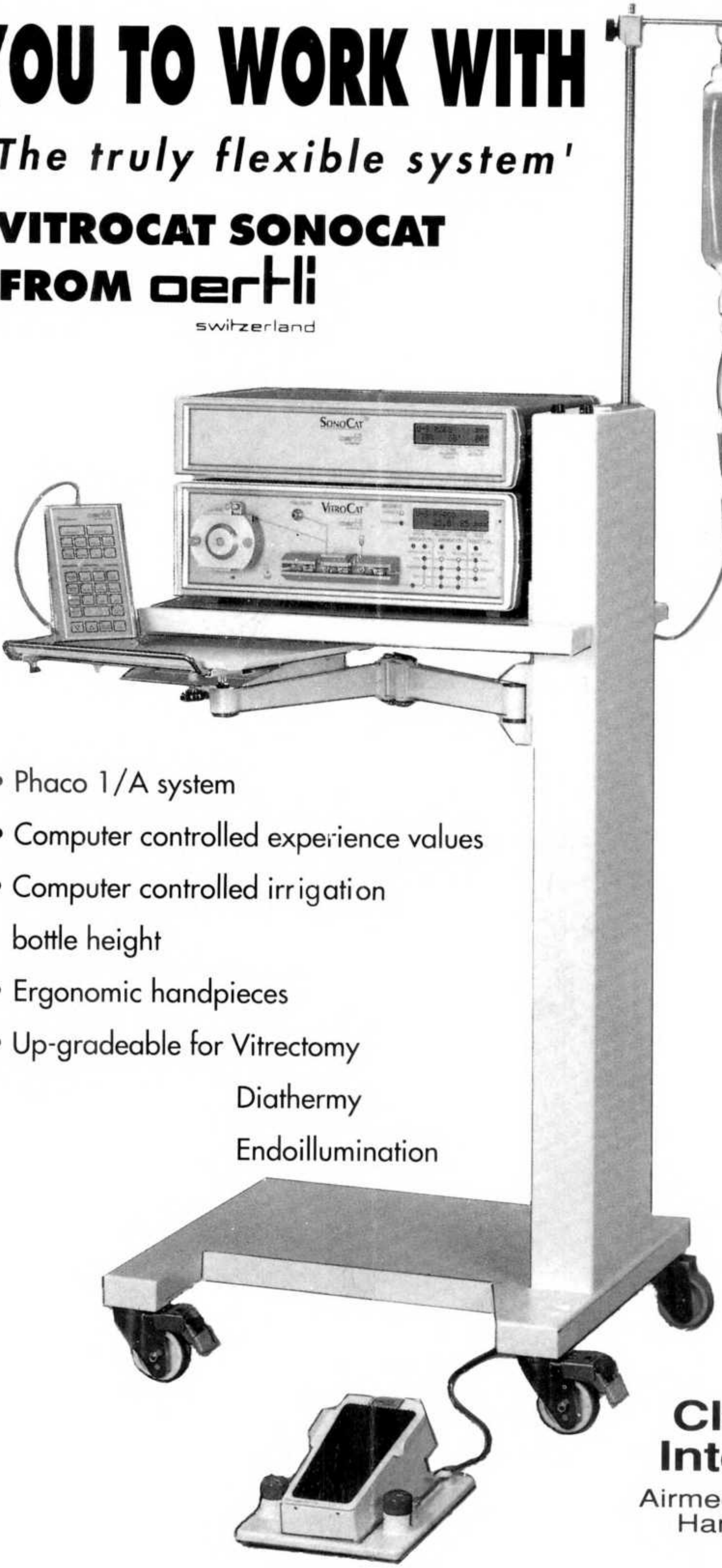
'The future today'



- Low light levels for patient comfort
- 40° or 20° fields
- Non-Mydriatic Fluorescein Angiography
- Non-Mydriatic ICG Angiography
- Increased depth of focus
- Real time recording
- Digital image processing and archiving

Now available for delivery

**THE
ULTIMATE
OPHTHALMOSCOPE
FROM
RODENSTOCK
THE SLO**



YOU TO WORK WITH THE BEST

'The truly flexible system'

VITROCAT SONOCAT
FROM oertli
switzerland

- Phaco 1/A system
- Computer controlled experience values
- Computer controlled irrigation bottle height
- Ergonomic handpieces
- Up-gradeable for Vitrectomy
  Diathermy
  Endoillumination

Canon

sonomed
ULTRASOUND

HAAG-STREIT AG

MÖLLER-WEDEL

LUNEAU
OPHTALMOLOGIE

G. RODENSTOCK
INSTRUMENTE GmbH

oertli
switzerland

Clement Clarke International Ltd

Airmed House, Edinburgh Way,
Harlow, Essex CM20 2ED

Tel 0279 414969
Fax 0279 635232
Tlx 81338

Did ed, BMJ, murder his wife?

Supposedly based on rumoured events in the life of Ernest Hart, a great but undervalued editor of the *BMJ,* Frank Danby's novel *Dr Phillips: a Maida Vale Idyll* was first published in 1887. Unlike many popular Victorian novels it is concisely plotted; its style is pithy; the characters are sympathetic and believable; and the author's presentation of Jewish life in the late nineteenth century is uncompromisingly honest. But is the character of "Dr Phillips" a portrait of Hart? In his introduction to the new Keynes Press edition Stephen Lock, present editor of the *BMJ,* places the novel in its literary and historical context and examines the character and achievements of Ernest Hart.

Beautifully printed and bound, and with illustrations by Tabitha Salmon, this edition of *Dr Phillips: a Maida Vale Idyll* will fascinate those interested in literature, history, and the *BMJ.*

Dr Phillips

A Maida Vale Idyll

FRANK DANBY

Published December 1989
Demy octavo; set in Monophoto Modern
and printed on Fineblade Cartridge paper,
xii + 285 pages + colour frontispiece
Limited edition of 300 copies
Inland £45.00; Abroad £49.00; USA $80.00
including postage, by air abroad
American Express, Mastercard, Visa credit cards
accepted. Please give full details.

British Medical Journal, (Keynes Press), PO Box 295,
London WC1H 9TE

THE
KEYNES
PRESS

British Journal of Ophthalmology, 1990, **74**, 437–439

Primary orbital liposarcoma: clinical and computed tomographic features

Alan A McNab, Ivan Moseley

Abstract

Liposarcoma of the orbit is rare. The clinical and radiological characteristics of two cases, of myxoid and pleomorphic types, are reported. In neither case was the histological diagnosis evident before surgery.

Primary orbital liposarcoma is extremely rare. Sixteen cases, mostly myxoid and none definitely identified as pleomorphic, have been reported in detail in the literature. The two patients described here are the fourth and fifth to be seen in the Orbital Clinic at Moorfields Eye Hospital since 1982. The preceding patients, all of whom had myxoid tumours, have been reported on previously.[1] To our knowledge the clinical and radiological features of pleomorphic liposarcoma arising in the orbit are described for the first time.

Case reports

CASE 1

A 69-year-old woman complained of progressive right proptosis over six months. She had vertical diplopia and difficulty in seeing colours clearly with the right eye. Her general health was excellent.

Her best corrected vision was 6/9 in the right eye and 6/6 left. She made four errors on the Ishihara test plates with the right eye, and was thought to have an afferent pupillary defect. The globe was displaced 9 mm forwards and 4 mm downwards. Ocular motility was restricted, particularly in elevation. A non-tender mass was palpable in the upper orbit. General examination was normal, as was a chest radiograph.

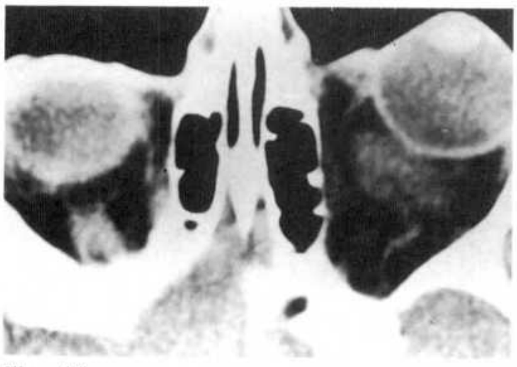


Figure 1A

Figure 1: Case 1. CT with intravenous contrast medium. Axial (A) and direct coronal (B) sections show a well defined, rounded, intraconal mass lying above the globe, which is not distorted. The mass extends posteriorly above the optic nerve (C). The orbit is not enlarged. The radiographic density of the mass is uniform, being intermediate between that of the vitreous and that of normal orbital fat – that is, it appears less dense than water. The more anterior coronal image (B) suggests a capsule of higher density.

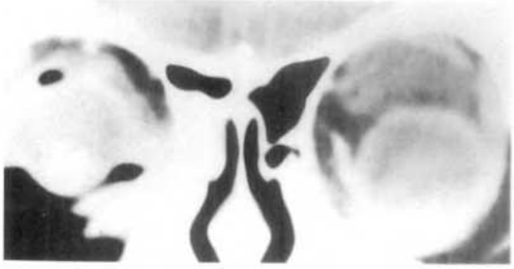


Figure 1B

Computed tomography (CT) of the orbits was obtained in sagittal and coronal planes after intravenous injection of iodinated contrast medium (Fig 1). A well defined, rounded intraconal mass of low density was shown, lying just above the globe.

The mass was explored via an upper lid skin incision, the levator palpebrae superioris and superior rectus muscles being retracted medially. Anteriorly the tumour was well circumscribed, but posteriorly it appeared to blend with the orbital fat. It was pale, yellow-grey, and petechial haemorrhages appeared on its surface as it was touched. The incisional biopsy specimen floated in 10% formaldehyde solution.

Histological examination revealed a tumour with numerous rounded spaces which on frozen section contained lipid. Some cells were spindle shaped and lay in a mucinous matrix, while others showed a signet ring form. There was nuclear hyperchromatism, scattered cells having enlarged, pleomorphic nuclei; some of the nuclei were vesicular. Numerous capillaries were present throughout the mass. The appearances were typical of a myxoid liposarcoma (Fig 2).

Over the next four weeks the proptosis increased by 2 mm. Orbital exenteration was performed, with removal of the upper lid and adequate clearance beyond the posterior margin of the tumour. There has been no evidence of recurrence for more than a year since surgery.

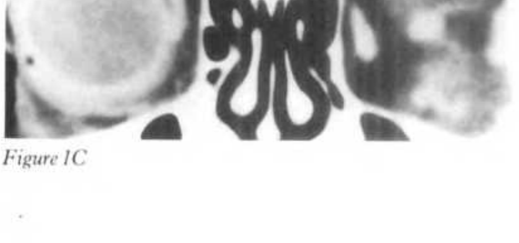


Figure 1C

Moorfields Eye Hospital, City Road, London EC1V 2PD
A A McNab
I Moseley

Correspondence to:
Dr I Moseley.

Accepted for publication 25 January 1990

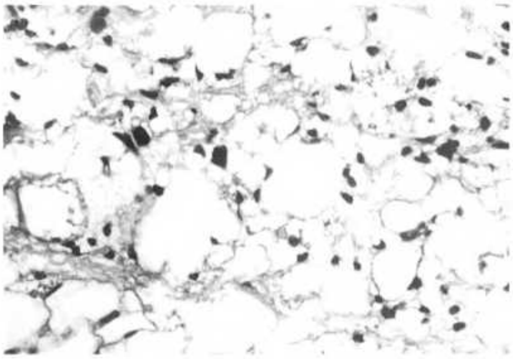


Figure 2: Case 1. Myxoid liposarcoma with nuclear hyperchromatism and occasional signet ring cells. The numerous clear spaces contained lipid on frozen section. (Haematoxylin and eosin, ×225.)

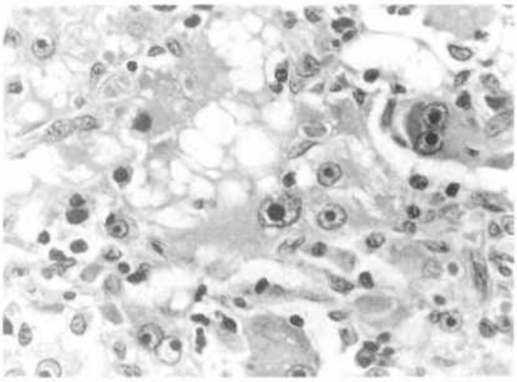


Figure 4: Case 2. Pleomorphic liposarcoma. The nuclei are variable in size, many having large, prominent nucleoli. The clear spaces also contained lipid on frozen section. (Haematoxylin and eosin preparation, ×225.)

CASE 2

A 52-year-old man noted blurred vision in the right eye seven months before his presentation to the orbital clinic, followed two months later by proptosis. His vision corrected to 6/9, but he had mild disc swelling and 3 mm of proptosis. This increased to 5 mm over 3 months, and he developed diplopia on left lateral gaze. He had no pain.

In the orbital clinic his best correctd acuity was 6/24 in the right eye and 6/5 left. He read all the Ishihara plates, but was slower on the right. There was a mild right relative afferent pupil defect. The globe was displaced 5 mm forwards and inferolaterally, with limited elevation and adduction. The optic disc was grossly swollen, with engorged retinal veins, but there were no choroidal folds. The upper lid was full. General examination and chest radiograph were normal.

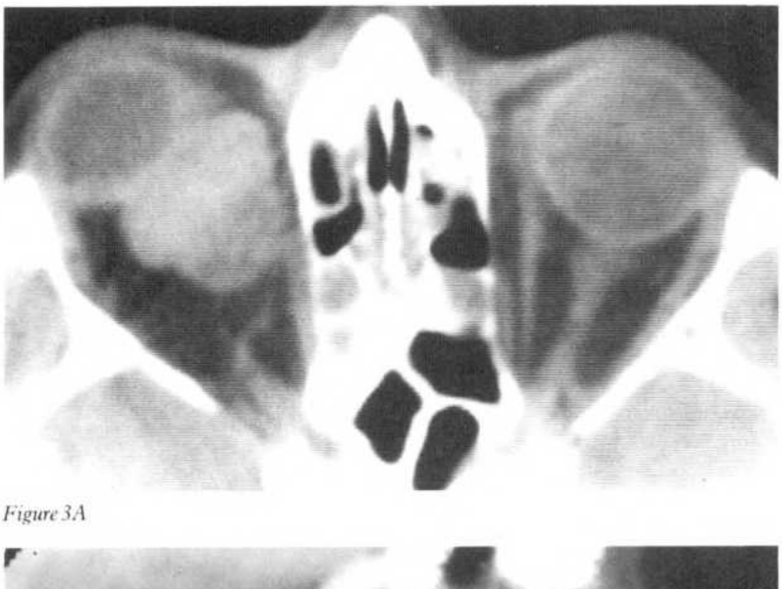


Figure 3A

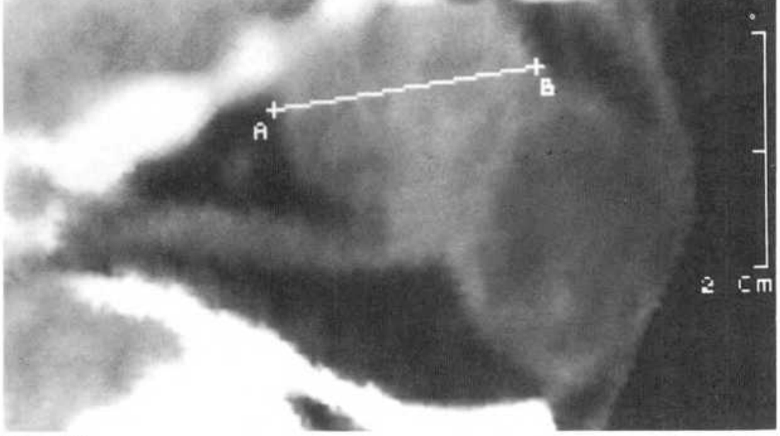


Figure 3B

Figure 3: Case 2. CT without intravenous contrast medium. Direct axial (A) and reformatted oblique parasagittal (B) images: a well defined, lobulated mass over 2 cm in diameter lies within the muscle cone, superomedial to the optic nerve, slightly flattening the globe. The mass is generally isodense with brain; its less dense posterior portion is still denser than the vitreous. The roof of the orbit is very thin, possibly eroded.

Plain films of the orbits also showed nothing abnormal, but CT showed a well defined mass within the muscle cone, containing areas of lower density within it (Fig 3).

At lateral orbitotomy a large, purplish, lobulated tumour was found intraconally, abutting the globe, the medial rectus muscle, and the upper surface of the optic nerve. It appeared to be well encapsulated, and was dissected free of the surrounding structures. A large artery entering its posterior pole was divided and the mass was removed in one piece.

Histological examination (Fig 4) disclosed a liposarcoma of extremely variable morphology, with numerous thin walled vessels, lipoblasts, and large, deeply eosinophilic giant cells. Mitotic figures were infrequent, but foci of inflammation and haemorrhage were present. There was no true capsule. The histological diagnosis was therefore pleomorphic liposarcoma.

The orbit was exenterated, together with the scar, but the lids were spared. Examination of the excised tissue showed a single nodule of tumour, less than 1 mm in diameter, well clear of the resection margin. One year later there was no evidence of local recurrence or distant metastasis.

Discussion

Because of its rarity liposarcoma does not usually enter into the differential diagnosis in patients with orbital masses. The 16 primary orbital liposarcomas reported in detail[1-12] affected men and women equally, their ages ranging from 5 to 77 years, mean 34.

Reports of the results of imaging are sketchy. Plain radiography commonly shows nothing abnormal, but it may show enlargement of the orbit, sometimes considerable, with thinning and inferior displacement of the floor.[1] Echography may indicate a relatively well defined, multiseptate lesion with non-specific areas of high echogenicity.[13] In the few patients who have undergone CT, none of whom had pleomorphic tumours, findings have varied from well defined, homogeneous lesions of soft tissue density, not evidently fatty,[11 13] to heterogeneous masses containing fat.[1] In two patients CT failed to reveal an identifiable mass, and in one of these T_2-weighted magnetic resonance imaging (MRI) showed abnormally high signal from part of the orbital fat, indicating its pathological nature.[1]

In our first patient the clue to the correct diagnosis was the low radiographic density of the lesion: fat is the only tissue component less dense than the water of the vitreous. Choristomas may contain fat, but are not characteristically retrobulbar, and benign lipomas of the orbit are exceedingly rare. Case 2 showed areas of lower density than brain but no clear evidence of fat. There were no radiological features indicating the malignant nature of the tumour in either patient. The short history and documented progression of symptoms and signs are, in retrospect, more suggestive.

Enziger and Weiss[14] divided primary liposarcomas into myxoid tumours (which form about half) and round cell, well differentiated, and dedifferentiated forms; a pleomorphic type is also described. Myxoid tumours usually have a gelatinous consistency, while poorly differentiated tumours are soft and haemorrhagic, with areas of necrosis and cyst formation. Of the primary orbital lesions reported most were myxoid; one showed predominantly round cells,[9] while another, described as lipocytic,[6] might have been categorised as pleomorphic.

Metastasis of liposarcoma to the orbit is also reported,[13 15] the commonest primary sites being the deep connective tissue planes of the thigh or retroperitoneum. In an obese patient like our case 1 it is possible, though unlikely, that a primary tumour went undetected.

The peak incidence of lipomas outside the orbit is between 40 and 60 years of age – that is, later than that of orbital lesions, probably reflecting their less critical location. Patients with myxoid tumours tend to be younger, and males are more commonly affected than females.[15]

Of the 16 well documented cases of primary orbital liposarcoma[1–12] six resulted in death. The consensus on treatment elsewhere in the body is wide local excision.[16–19] Radiotherapy affords little benefit in the better differentiated liposarcomas, but successes have been reported with poorly differentiated tumours.[16] Chemotherapy has not generally been helpful, though Gottlieb *et al*[20] reported remission in three patients.

Both the tumours described here were well defined on CT and appeared relatively well encapsulated at surgery. However, the 'capsule' represents compressed orbital tissues; there is no true capsule between the neoplastic tissue and the normal structures. Three patients previously operated upon in this hospital[1] have now been followed up for from two to five years without evidence of tumour recurrence or dissemination.

Prognosis of liposarcomas elsewhere in the body has been related to histology. Thus in a series of 77 patients treated by surgical excision, 27 of whom also received radiotherapy, the 10-year survival was 12 of 20 with myxoid tumours, but only 1 of 24 with round cell or pleomorphic lesions. Site, size, and adequacy of excision were all important factors.[21] The rational approach to orbital liposarcoma would therefore appear to be wide local excision, which will usually necessitate exenteration or even midfacial resection. In an elderly patient with a mxyoid or well differentiated tumour local excision is justifiable.

AA McNab was supported by the OPSM fellowship of the Royal Australian College of Ophthalmologists.

1 Lane CM, Wright JE, Garner A. Primary myxoid liposarcoma of the orbit. *Br J Ophthalmol* 1988; 72: 912–7

2 Strauss M. Liposarkom der recten Orbita *Dtsch Med Wochenschr* 1911; 37: 239

3 Stout AP. Liposarcoma – the malignant tumour of lipoblasts. *Ann Surg* 1944, 119: 86–107.

4 Quéré MA, Camain R, Baylet R Liposarcome orbitaire. *Ann Oculist (Paris)* 1963; 196: 994–1003

5 Cilotti P. Su di particolare forma di liposarcoma dell'orbita con conspicue variazioni morfologiche durante la sua evoluzione *Ann Oftal Oculistica* 1964, 90: 325–37

6 Mortada A Rare primary orbital sarcomas. *Am J Ophthalmol* 1969, 68: 919–25.

7 Henderson JW *Orbital tumors* Philadelphia Saunders, 1973 262–7.

8 Schroeder W, Dastendieck H, von Domarus D Primares myxoides Liposarkom der Orbita klinscher und histopathologischer Fallbericht. *Ophthalmologica* 1976, 172: 337–45.

9 Kimura Y, Nagato M, Yamabe H A case of orbital liposarcoma *Fol Ophthalmol Jpn* 1978, 29: 983–8.

10 Jakobiec FA, Jones IS. In: Duane TD, ed. *Clinical ophthalmology*. Hagerston. Harper and Row, 1982; 2: 17–9

11 Naeser P, Mostrom U Liposarcoma of the orbit a clinicopathological case report. *Br J Ophthalmol* 1982; 66: 190–3

12 Malan P, Baldet P, Arnaud B Primary orbital liposarcoma Clinicopathological case report and review of the literature *Orbit* 1983; 2: 99–105.

13 Nasr AM, Ossoinig KC, Kersten RF, Blodi FC. Standardized echographic-histopathologic correlations in liposarcoma. *Am J Ophthalmol* 1985; 99: 193–200

14 Enziger FM, Weiss SW. *Soft tissue tumors*. St Louis: Mosby, 1973

15 Abdalla MI, Ghaly AF, Hosni F. Liposarcoma with orbital metastases. *Br J Ophthalmol* 1966, 50: 426–8

16 Enterline HT, Culberson JD, Rochlin DB, Brady LW. Liposarcoma a clinical and pathological study of 53 cases *Cancer* 1960; 13: 932–50.

17 Pack GT, Pierson JC. Liposarcoma: a study of 105 cases. *Surgery* 1954; 36: 687–712.

18 Spittle ME, Newton KA, McKenzie DH Liposarcoma A review of 60 cases *Br J Cancer* 1970, 24: 696–704

19 Kinne DW, Chu FCH, Huvos AG, Yagoda A, Fortner JG Treatment of primary and recurrent retroperitoneal liposarcoma. Twenty-five-year experience at Memorial Hospital *Cancer* 1973; 31: 53–64.

20 Gottlieb JA, Baker LH, Quagliana JM, *et al* Chemotherapy of sarcomas with a combination of adriamycin and dimethyl triazeno imidazole carboxamide. *Cancer* 1972, 30: 1632–8

21 Kindblom LG, Angervall L, Svendsen P Liposarcoma a clinicopathological, radiographic and prognostic study. *Acta Pathol Microbiol Immunol Scand (A)* 1975 suppl 253.

British Journal of Ophthalmology, 1990, 74, 440–442

Inflammation of the retinal pigment epithelium: a unique presentation of ocular schistosomiasis

A Jane Dickinson, A Ralph Rosenthal, Karl G Nicholson

Abstract

We report the first case of inflammation of the retinal pigment epithelium (RPE) caused by *Schistosoma mansoni* and discuss its possible pathogenesis. This is of particular interest because the lesions resembled those found in acute multifocal placoid pigment epitheliopathy (AMPPE).

Schistosomiasis affects 200 million people throughout the world, and its associated morbidity and mortality are thus of major importance. On contact with infected water it takes only minutes for cercarciae to enter skin, though the eyeball resists penetration.[1] The young organisms quickly reach cutaneous venules, and thereafter remain intravascular. They must reach the liver in order to mature, and they then migrate into the portal caval venous circulation or occasionally pulmonary arterioles, where they mate and lay eggs.

The chief lesion of schistosomiasis is an intravascular obstructive process: either a granuloma or a hypersensitive vascular response, and as only mature worms or ova excite this response it is usually confined to the portal caval venous circulation and adjacent viscera, reactions to worms or ova elsewhere being defined as ectopic.[2] Symptomatic ectopic infections with *S mansoni* are particularly rare,[3,4] though necropsy studies suggest that asymptomatic lesions of the central nervous system may be common.[5]

Case report

A 17-year-old man presented with profound right visual deterioration and an itchy eruption on his forehead, both of two weeks' duration. He had recently returned from Tanzania, where he previously lived, and recalled a febrile illness with myalgia and diarrhoea shortly after swimming in Lake Victoria six weeks previously. He had taken no antimicrobials in the recent past.

Examination revealed a papular eruption over the left forehead (Fig 1). from which a small biopsy was taken. Visual acuity was 6/60 right eye and 6/5 left eye, with a right afferent pupil defect and a mild right iridocyclitis. Funduscopy of the right eye revealed optic disc swelling and multiple creamy lesions confined to the superotemporal quadrant, clinically at the level of the RPE, with intraretinal exudates round the fovea (Fig 2). On fluorescein angiography the creamy lesions showed early masking of the choriocapillaris (Fig 3), and there was hyperfluorescence of the superotemporal disc margin followed by generalised disc leakage. By four minutes all creamy lesions were hyperfluorescent, some with persistent central masking (Fig 4), but the macular exudates did not fluoresce. The left eye was normal and a general examination showed nothing abnormal.

Histological examination of the skin biopsy specimen showed two ova of *Schistosoma mansoni* with numerous eosinophils. The patient had a

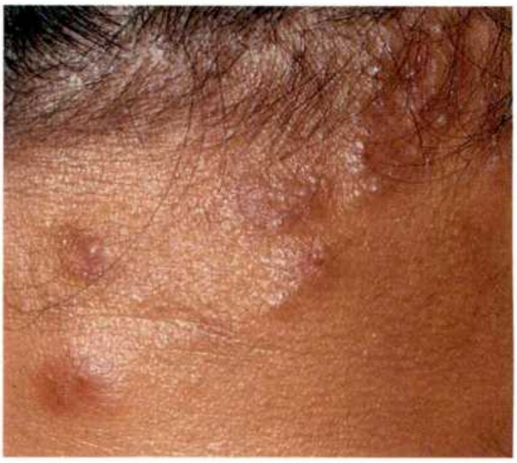


Figure 1: Papular eruption over the left forehead, extending to the midline.

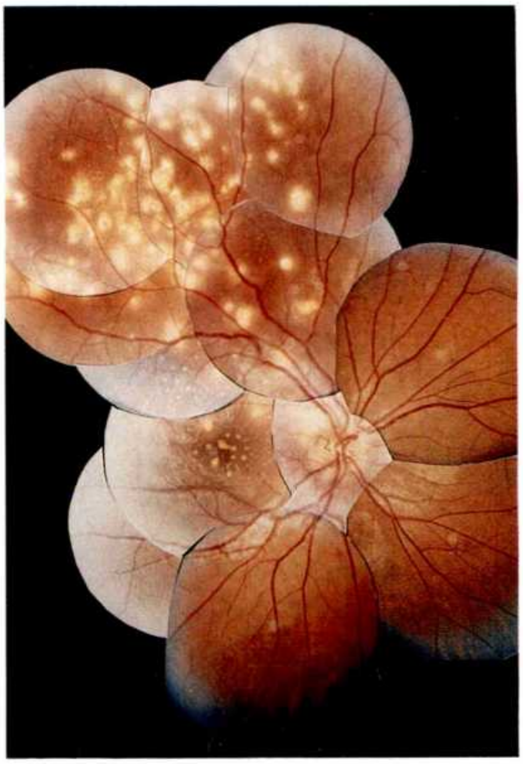


Figure 2: Right fundus, showing sectoral distribution of creamy lesions, clinically at the level of the RPE, with intraretinal exudates at the fovea and slight swelling of the optic disc.

University Department of Ophthalmology, Leicester Royal Infirmary, Leicester
A J Dickinson
A R Rosenthal

Department of Infectious Diseases, Groby Road Hospital, Leicester
K G Nicholson

Correspondence to:
Dr A Jane Dickinson,
Department of Ophthalmology, Leicester Road Infirmary, Infirmary Close, Leicester LE1 5WW.

Accepted for publication 23 January 1990

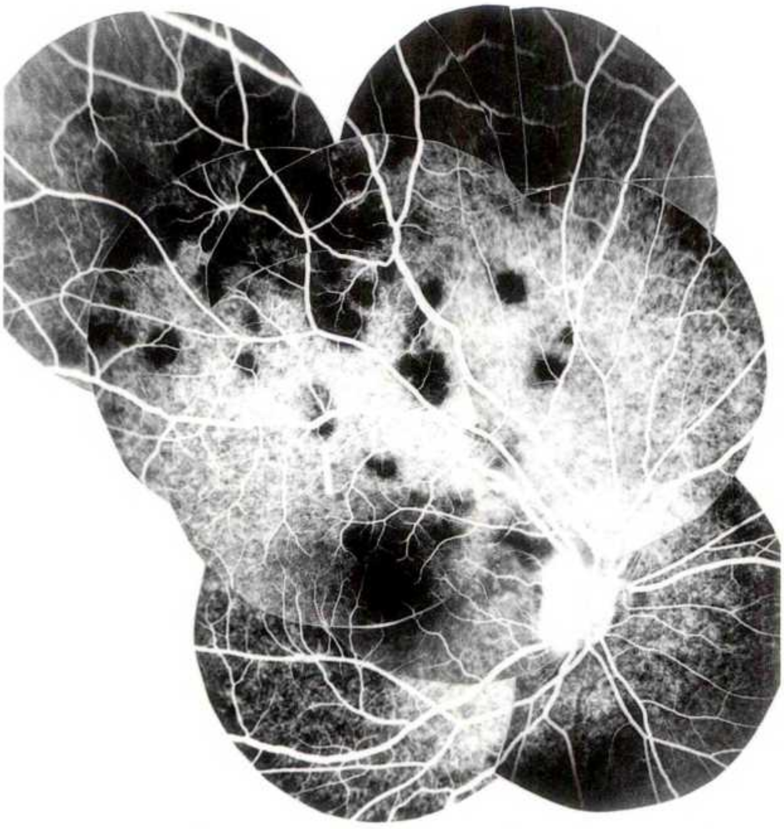


Figure 3: Arteriovenous phase of fluorescein angiogram showing masking of the choriocapillaris by the RPE lesions. (Arrow indicates lesion shown in Fig 4.)

47% eosinophilia (leucocytes $5\cdot3\times10^9$/l). Stool examination revealed numerous *S mansoni* ova; urine examination gave negative results. The enzyme-linked immunosorbent assay for schistosomal antibody was positive at level 1, later rising to level 4. Chest *X*-ray and liver function tests were normal, and serological tests negative for toxocara, toxoplasma, and syphilis.

Six weeks after treatment with praziquantel (40 mg/kg body weight given once) the skin lesions had resolved. The right visual acuity had improved to 6/5, with resolution of the disc swelling and exudates, and the fundal lesions had evolved into chorioretinal, centrally pigmented scars (Fig 5). Repeat fluorescein angiography showed no disc leakage, but was otherwise unchanged. He has remained well since.

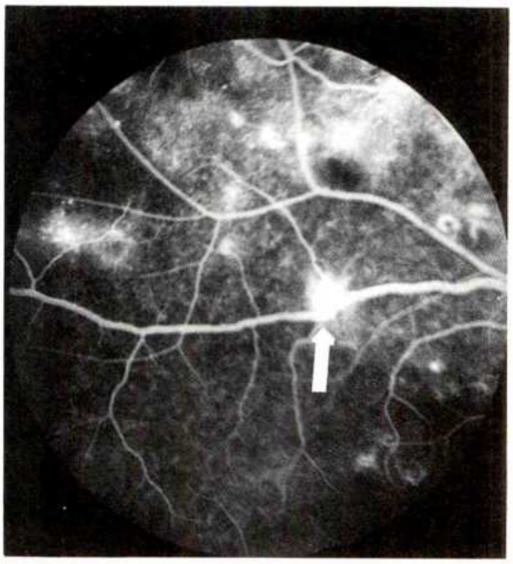


Figure 4: Fluroescein angiogram after six minutes, with most initially masked areas now hyperfluorescent. (Arrow indicates lesion seen in Fig 3.)

Discussion

The skin lesion in this patient, which has been reported on elsewhere,[6] is likely to have contained numerous ova. This suggests ectopic worm migration, with local oviposition, rather than egg embolism.

The ocular lesions may be explained in two ways. It is most probable that the disease was primarily within the choroidal circulation, with either ova, worms, or a hypersensitive response in the choriocapillaris causing secondary ischaemia or inflammation in the RPE and disc. Choroidal granulomas round *S mansoni* ova have been reported,[7] and in an experimental model of ascarid endophthalmitis RPE lesions developed secondarily to an eosinophilic choroiditis and far from any organism.[8]

Alternatively the disease may have primarily affected the retina. The sectoral distribution of lesions round a single retinal vessel is more suggestive of retinal than choroidal disease, and the exudates indicate retinal involvement, though they may have been a secondary phenomenon. If the lesions were centred on ova, then either eggs were laid by a worm at the disc or mechanical factors directed all eggs to one vessel. The disc oedema and afferent pupil defect certainly imply disc inflammation, but as female worms measure 0·2 × 25 mm it is hard to envisage a worm in the vessels at the disc without evidence of vessel obstruction.

The creamy lesions in this patient had the clinical and angiographic appearances of those found in AMPPE. Although it is still argued that this may be a primary inflammation of the RPE, the more favoured hypothesis is that it is due to immune-complex induced vascular obstruction of the choriocapillaris with subsequent RPE ischaemia.[9,10] We believe that vascular obstruction of the choriocapillaris either by ova or a hypersensitivity response caused the RPE lesions in this patient.

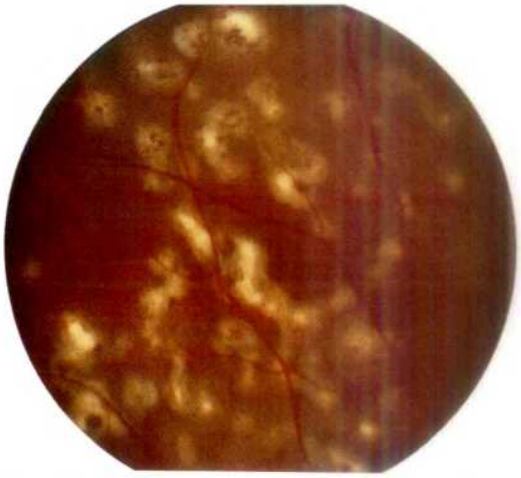


Figure 5: Superotemporal area of right fundus two months after treatment, with semiconfluent chorioretinal scars.

Given the scale of schistosomiasis it is surprising that both extragenital and intraocular lesions are so rarely reported.[11-13] Abboud *et al*'s study of 150 patients detected no ocular lesions definitely attributable to schistosomiasis,[1] though examination details are lacking. Nevertheless, necropsy studies have demonstrated ova in up to 56% of brains,[3] and, as fundi may not be routinely examined and small granulomas hard to visualise,[8] intraocular infection may be more common than is apparent.

1 Abboud IA, Hanna LS, Ragab HAA Experimental ocular schistosomiasis *Br J Ophthalmol* 1971, 55: 106–15.
2 Faust EC. An inquiry into the ectopic lesions in schistosomiasis *Am J Trop Med Hyg* 1948, 28: 175–99
3 Scrimgeour EM, Gajdusek DC Involvement of the central nervous system in *Schistosoma mansoni* and *S haematobium* infection A review *Brain* 1985; 108: 1023–38
4 Chityo ME. Schistosomal involvement of the choroid plexus. *Cent Afr J Med* 1972, 18: 45–7.
5 Pittella JEH, Lana-Peixoto MA Brain involvement in hepatosplenic schistosomiasis mansoni *Brain* 1981, 104: 621–32.
6 Milligan A, Burns DA Ectopic cutaneous schistosomiasis and schistosomal ocular inflammatory disease. *Br J Dermatol* 1988; 119: 793–8
7 Pittella JEH, Orefice F Schistosomotic choroiditis II Report of first case *Br J Ophthalmol* 1985; 69: 300–2
8 John T, Barsky HJ, Donnelly JJ, Rockey JH Retinal pigment epitheliopathy and neuroretinal degeneration in ascarid-infected eyes. *Invest Ophthalmol Vis Sci* 1987, 28: 1583–98.
9 Young NJA, Bird AC, Sehmi K Pigment epithelial diseases with abnormal choroidal perfusion *Am J Ophthalmol* 1980, 90: 607–18
10 Lyness AL, Bird AC Recurrences of acute posterior multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1984, 98: 203–7
11 Newton JC, Kanchanaranya C, Previte LR Jr Intraocular *Schistosoma mansoni* *Am J Ophthalmol* 1968; 65: 774–8.
12 Jacyk WK, Lawande RV, Tulpule SS. Unusual presentation of extragenital cutaneous schistosomiasis mansoni *Br J Dermatol* 1980; 103: 205–8
13 Orefice F, Simal CJR, Pittella JEH. Schistosomotic choroiditis I Funduscopic changes and differential diagnosis *Br J Ophthalmol* 1985, 69: 294–9

British Journal of Ophthalmology, 1990, 74, 443–444

Acute retinal necrosis as a novel complication of chickenpox in adults

T Matsuo, M Koyama, N Matsuo

Department of Ophthalmology, Okayama University Medical School, Okayama City, Japan
T Matsuo
M Koyama
N Matsuo

Correspondence to:
Toshihiko Matsuo, MD, Department of Ophthalmology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama City, Okayama 700, Japan.

Accepted for publication 4 January 1990

Abstract

Three patients in their 20s suffered from chickenpox while in an immunocompromised state: one in pregnancy, one during a long course of corticosteroid for severe nephrotic syndrome, and the third with repeated upper airway infection due to bronchiectasis. They developed acute retinal necrosis about three weeks after the onset of chickenpox. Since acute retinal necrosis threatens sight, this unusual complication of chickenpox in adults needs serious consideration.

Chickenpox is well known to have various complications.[1] About 15% of adults with chickenpox develop primary varicella pneumonia. Central nervous system complications such as postinfectious encephalitis occur most frequently in children. Other rare complications are myocarditis, nephritis, nephrosis, arthritis, thrombocytopenic purpura, orchitis, appendicitis, and subclinical hepatic involvement. Corneal lesions, iritis, and optic neuritis have been recognised as ophthalmological complications. Chickenpox occurring in adults, especially in immunocompromised patients, usually runs a more severe course than in children.

Acute retinal necrosis is characterised by extending necrotic lesions of the retina and retinal arteritides coupled with uveal inflammation (iridocyclitis). If untreated, it results in permanent visual reduction or loss.[2-4] It is caused by infection with varicella zoster or herpes simplex type 1 virus.[5,6] We report hereon three immunocompromised adult patients who developed acute retinal necrosis about three weeks after the onset of chickenpox.

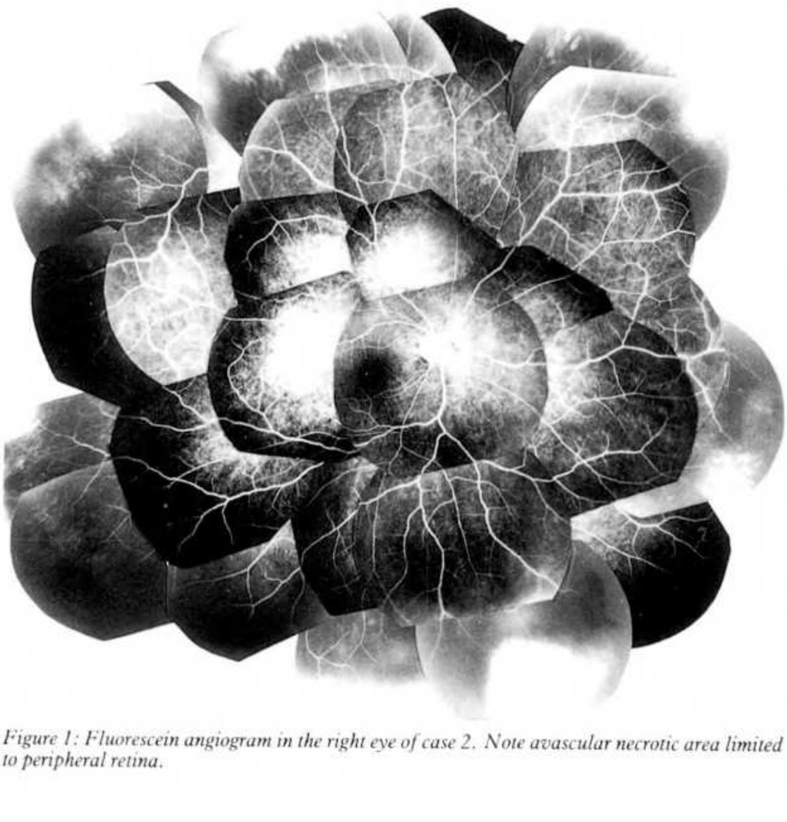


Figure 1: Fluorescein angiogram in the right eye of case 2. Note avascular necrotic area limited to peripheral retina.

Case reports

CASE 1

A 26-year-old woman in the tenth month of gestation experienced redness and blurred vision in the right eye about one month after the onset of chickenpox. The best corrected visual acuity was 20/200 in the right eye and 20/30 in the left. The intraocular pressure was 10 mmHg in both eyes. She showed confluent yellowish white retinal exudates in the peripheral fundus of both eyes coupled with iridocyclitis: 3+ keratic precipitates, 3+ aqueous cells, 2+ vitreous cells in the right eye, and 1+ keratic precipitates, 2+ aqueous cells, 1+ vitreous cells in the left eye. A healthy baby, the patient's second child, was delivered by uncomplicated caesarean operation two weeks later. Immediately afterwards intravenous administration of acyclovir 500 mg/day for two weeks and prednisolone tapered from 200 mg/day was started. The fundus lesion resulted in retinochoroidal degeneration in the following three weeks, and the visual acuity in both eyes returned to 20/20.

CASE 2

A 20-year-old woman noticed redness in the right eye about three weeks after the onset of severe chickenpox. She had been taking 20 mg/day of prednisolone for severe nephrotic syndrome during the preceding three years. The best corrected visual acuity was 20/20 in both eyes, and the intraocular pressure was 18 mmHg in both eyes. Examination disclosed a necrotic retinal area limited to the peripheral fundus in the right eye (Fig 1), which was associated with anterior segment inflammation as 1+ keratic precipitates, 2+ aqueous cells, and 2+ vitreous cells. The left eye appeared normal. She received a drip infusion of acyclovir 1500 mg/day for two weeks and prednisolone tapered from 200 mg/day. The necrotic lesion resolved within three weeks.

CASE 3

A 29-year-old man developed severe chickenpox during admission to hospital for bronchiectasis. He noticed blurred vision and floating spots in

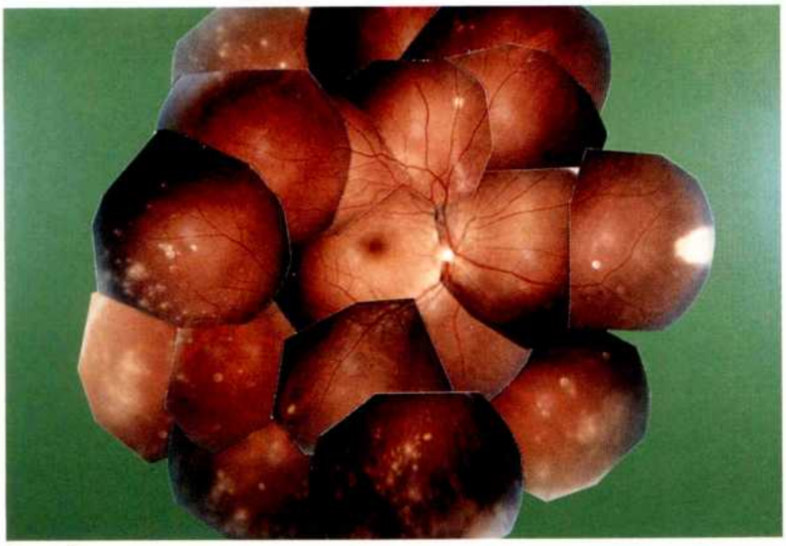


Figure 2A

Figure 2: Fundus photographs of the right eye of case 3. A: On initial visit. B: One week later. Note necrotic retinal lesions extending in one week.

the right eye 20 days after the onset of chickenpox. The best corrected visual acuity was 20/15 in both eyes, and the intraocular pressure was 15 mmHg in both eyes. The fundus in the right eye showed a typical picture of acute retinal necrosis (Fig 2A), together with iridocylitis: 1+ keratic precipitates, 3+ aqueous cells, and 1+ vitreous cells. The left eye was normal. He received a drip infusion of acyclovir 1500 mg/day for two weeks and gradual tapering of prednisolone from 200 mg/day. The necrotic lesion of the retina extended gradually (Fig 2B), but finally resolved in three weeks. Two years previously he had undergone left orchidectomy and radiation for testicular seminoma. Subsequently he was prone to bronchitis and low grade fever.

Discussion

All three patients were in their 20s and in a somewhat immunocompromised state: the woman in case 1 was in the tenth month of gestation, the woman in case 2 had been taking steroids for three years, and the man in case 3 had had repeated episodes of bronchitis and low grade fever after successful treatment for testicular seminoma. All three patients had severe chickenpox which resolved without complications but developed acute retinal necrosis about three weeks to one month after the onset of the chickenpox. Initial symptoms of acute retinal necrosis were blurred vision, floating spots, and/or redness. Both eyes were involved in one patient, but only one eye in the others.

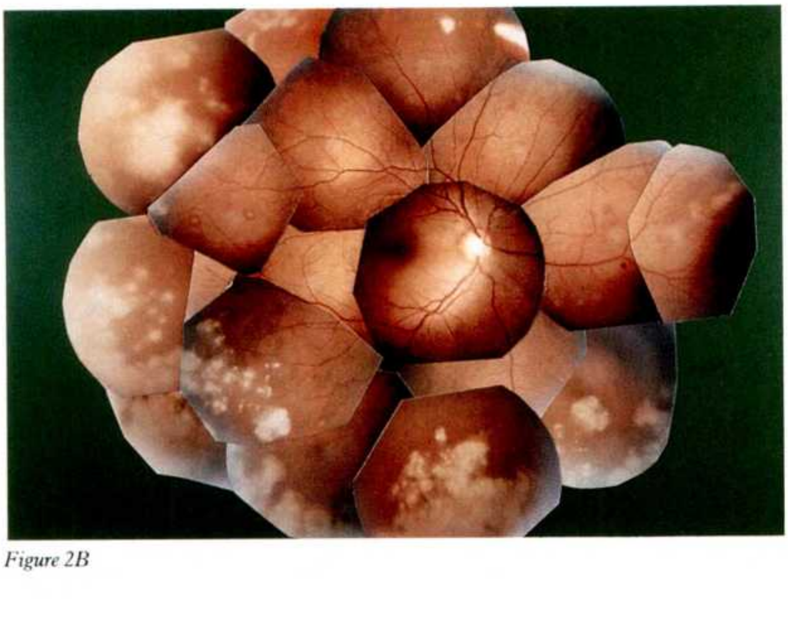


Figure 2B

Acute retinal necrosis is classified clinically into fulminant and mild types as we proposed recently.[7] Isolated retinal necrotic lesions occurring initially in the peripheral fundus become confluent and extend rapidly to the posterior pole in the fulminant type, leading to marked visual reduction, in spite of intensive treatment with acyclovir and cortiosteroid. In contrast patients with the mild type of acute retinal necrosis showed slowly progressive, but self limiting necrotic lesions of the retina and preserved good vision with the drug therapy. All these three patients showed the mild type of acute retinal necrosis following chickenpox and regained good visual acuity after the intraocular inflammation had subsided. As we discussed in the recent report,[7] administration of acyclovir and steroid seems to reduce the rate of its late complications, such as retinal tears. Thus it is important to detect acute retinal necrosis, regardless of mild or fulminant type, as early as possible and to start appropriate therapy. Acute retinal necrosis should be kept in mind as a possible complication when patients with chickenpox complain of eye symptoms.

It is interesting to note that the period from the onset of chickenpox to acute retinal necrosis was about three weeks in all three patients. Thus the chickenpox had subsided when the acute retinal necrosis began. Herpes group virus has been found electron microscopically in the retina with acute retinal necrosis obtained by biopsy.[4 5] In immunocompromised patients varicella-zoster virus would tend to be more easily reactivated in the retina, leading to acute retinal necrosis.[1]

1 Ray CG. Chickenpox (varicella) and herpes zoster. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JB, eds. *Harrison's principles of internal medicine*. 10th ed. New York: McGraw-Hill, 1983: 1121–5.
2 Urayama A, Yamada N, Sasaki T, *et al*. Unilateral acute uveitis with retinal periarteritis and detachment. *Jpn J Clin Ophthalmol* 1971; **25:** 607–19.
3 Willerson D, Aaberg TM, Reeser FH. Necrotizing vaso-occlusive retinitis. *Am J Ophthalmol* 1977; **84:** 209–19.
4 Young NJA, Bird AC. Bilateral acute retinal necrosis. *Br J Ophthalmol* 1978; **62:** 581–90.
5 Culbertson WW, Blumenkranz MS, Haines H, Gass JDM, Mitchell KB, Norton EWD. The acute retinal necrosis syndrome. 2. Histopathology and etiology. *Ophthalmology* 1982; **89:** 1317–25.
6 Freeman WR, Thomas EL, Rao NA, *et al*. Demonstration of herpes group virus in acute retinal necrosis syndrome.*Am J Ophthalmol* 1986; **102:** 701–9.
7 Matsuo T, Nakayama T, Koyama T, Koyama M, Matsuo N. A proposed mild type of acute retinal necrosis syndrome. *Am J Ophthalmol* 1988; **105:** 579–83.

British Journal of Ophthalmology, 1990, **74**, 445–446

Frontal bone epidermoid – a rare cause of proptosis

C R Chowdury, C M Wood, P R Samuel, J Richardson

Abstract

Frontal bone epidermoid is a rare condition which may present with proptosis, extraocular muscle imbalance, or loss of vision. Clinically and on plain radiographs an epidermoid may be confused with commoner conditions such as frontal mucocoele. However, the characteristic CT scan appearance, which shows a bone cyst with similar density to brain tissue, should lead to an accurate diagnosis and appropriate surgical management.

Frontal bone epidermoid is an extremely rare condition with less than 30 authentically documented cases reported in the literature. The presentation is generally with facial asymmetry, unilateral proptosis, extraocular muscle imbalance, and occasionally visual loss.[1,2] The clinical and plain radiographic features of the condition show a certain similarity with frontal sinus mucocoele,[3,4] which can lead to diagnostic confusion and inappropriate surgical treatment. Fortunately the specific CT scan appearance enables an accurate diagnosis to be made.

We report a single case of a frontal bone epidermoid which illustrates the typical clinical, plain radiographic, and CT scan features of the disease.

Case report

A 57-year-old male presented with progressive proptosis and facial asymmetry. He was otherwise well, with no history of headache, paranasal sinus disease, or trauma. His right visual acuity was 6/6, and he had an irreducible, non-pulsatile right proptosis and hypotropia, but no frank diplopia. Further examination of his eyes, ears, nose, and throat and a general examination revealed no other abnormality.

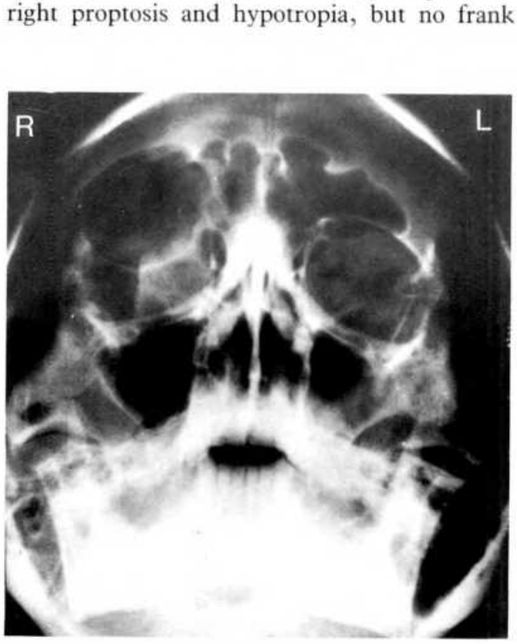


Figure 1: Plain x-ray of sinuses (occipitofrontal view) showing cavitation in the right frontal bone

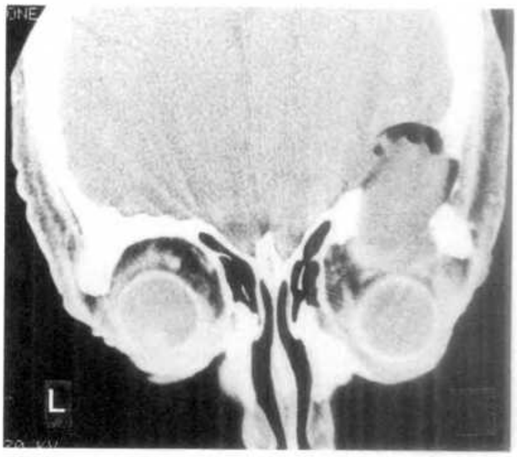


Figure 2: CT scan with coronal projection showing destruction of the roof of the right orbit and downward displacement of the globe by the epidermoid, which can be seen to have a similar tissue density to brain.

A plain *x*-ray of the sinuses showed a rounded, sharply circumscribed, bony defect in the right frontal bone with marginal sclerosis (Fig 1). The CT scan coronal (Fig 2) and axial (Fig 3) projections showed destruction of the roof of the orbit, with downward displacement of the globe, and defects in the anterior and posterior surfaces of the frontal bone. The wall of the cyst was well defined by contrast media, and the contents had a similar density to that of brain tissue.

Under a general anaesthetic a curved incision extending from the medial canthus through the eyebrow to the temple was made. A large cyst (3·5 cm in diameter) occupied a cavity in the frontal bone, communicating via the bony defects noted on the CT scan with the orbit and anterior cranial fossa. The dura and the orbital periosteum were intact. The cyst was removed, and a Silastic drainage tube into the nose was left in situ for two months. Postoperatively he was treated with cefuroxime and metronidazole.

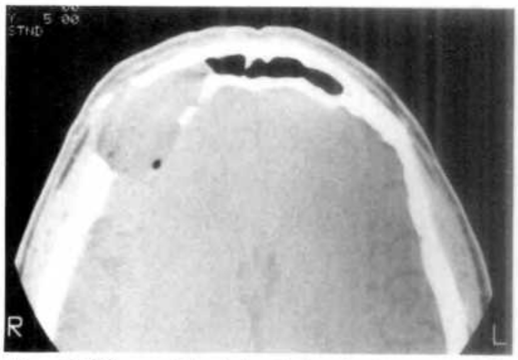


Figure 3: CT scan with axial projection showing erosion of the anterior and posterior surfaces of the frontal bone by the epidermoid.

Department of Ear, Nose, and Throat, Royal Infirmary, Sunderland
C R Chowdury
P R Samuel

Sunderland Eye Infirmary
C M Wood
J Richardson

Correspondence to:
Mr Christopher M Wood, FRCSE, Eye Infirmary, Queen Alexandra Road, Sunderland, Tyne and Wear SR2 9HP.

Accepted for publication
8 February 1990

Histology of the cyst revealed an epithelial lining with a central mass of keratin. The proptosis has resolved completely and he has made a full recovery.

Discussion

Epidermoids result from the proliferation of epithelial elements in an inappropriate site. Primary epidermoids arise from embryonal inclusions of epithelial cell rests at sites of fusion of embryonal ectoderm. Secondary epidermoids may result from a postnatal event such as traumatic implantation of cells, cell migration, or metaplasia.[5]

Histologically an epidermoid consists of a cyst with a squamous epithelium lining containing keratin, lipid laden histiocytes, cholesterol, and a fibrous stroma.[5] The name cholesteatoma is frequently applied to such lesions,[3 4] though it is a misleading term which can lead to confusion with other similar pathological conditions and thus is best avoided.[5] The presence of an epithelial cell lining enables an epidermoid to be differentiated from a cholesterol granuloma,[1] and the absence of any mesodermal elements differentiates it from a dermoid cyst.[5]

The clinical presentation of an epidermoid can easily be confused with a frontal sinus mucocoele,[3 4] as, typically, the patient experiences vague headaches, a progressive proptosis with hypotropia, and sometimes visual loss. In such cases an incorrect diagnosis can lead to an inadequate surgical approach and incomplete removal, putting the patient at risk from recurrences[6] as long as 40 years after the original surgery[7] and, on rare occasions, malignant transformation.[8]

1 Parke DW, Font RL, Boniuk M, McCary JA Cholesteatoma of the orbit. *Arch Ophthalmol* 1982, 100: 612–6

2 Carey PC Epidermoid and dermoid tumours of the orbit *Br J Ophthalmol* 1958, 42: 225–39

3 Campanella RS, Caldarelli DD, Freiberg SA Cholesteatoma of the frontal sinus.*Ann Otol Rhinol Laryngol* 1979, 88: 518–23.

4 Calcaterra TC, Schwartz HE. Cholesteatoma of the frontal sinus. *Ophthalmology* 1976; 82: 579–81

5 Hopp ML, Montgomery WW. Primary and secondary keratomas of the frontal sinus. *Laryngoscope* 1984, 94: 628–32

6 Thacker EA Epidermoid tumours of the frontal bone, sinus and orbit *Arch Otolaryngol* 1950; 51: 400–13

7 Holt GR, Holt JE, Davis WE. Late recurrence of a frontal sinus cholesteatoma *Ann Otol* 1977, 86: 852–5

8 Maniglia AJ, Villa L Epidermoid carcinoma of the frontal sinus secondary to cholesteatoma *Ophthalmology* 1977; 84: 112–5.

LETTERS TO THE EDITOR

Mollicute-like organisms

SIR,—It was a thrill for me to read the article 'Chronic orbital inflammatory disease: parasitisation of orbital leucocytes by mollicute-like organisms' by Wirostko, Johnson, and Wirostko.[1] Their thesis in an important series of papers is that cell wall defective bacterial forms may play some role in human ocular pathology.

Some years ago I also published a series of papers on this topic, two of which[2,3] were submitted as a thesis to the American Ophthalmological Society (but not accepted). I continue to believe that the last word has yet to be written and that other researchers such as Dr Wirostko and colleagues may well vindicate the bibliography below.

It is interesting that my coworker, Carolyn Barth, successfully defended a PhD thesis on this same work at Wayne State University. At the time I felt, and to a certain extent still do, that pure scientists are more receptive to ideas which contest their preconceived notions than are my senior ophthalmological colleagues.

PHILIP C HESSBURG
15401 East Jefferson,
Grosse Pointe Park,
Michigan 48230,
USA

1 Wirostko E, Johnson L, Wirostko B Chronic orbital inflammatory disease. parasitisation of orbital leucocytes by mollicute-like organisms *Br J Ophthalmol* 1989; 73: 865–70.
2 Hessburg PC Studies on uveitis· part I Aqueous studies *Henry Ford Hosp Med J* 1977, 25: 255–80
3 Hessburg PC Studies on uveitis part II. Hypotheses with case reports *Henry Ford Hosp Med J* 1978; 26: 17–38.
4 Hessburg PC, Mattman LH, Barth C, Dutcheshen LT. Aqueous microbiology: the possible role of cell wall deficient bacteria in uveitis *Henry Ford Hosp Med J* 1969, 17: 177–94
5 Dutcheshen LT, Hessburg PC A microtechnique for the isolation of cell wall deficient organisms from very small samples. *Henry Ford Hosp Med J* 1973, 21: 31–8.
6 Barth CL, Judge MS, Mattman LH, Hessburg PC. Isolation of an acid-fast organism from the aqueous humor in a case of sarcoidosis *Henry Ford Hosp Med J* 1979; 27 (2).
7 Dominique GJ Cell wall-deficient bacteria: basic principles and clinical significance. In Barth CL, Hessburg PC, eds. *Role of cell wall-deficient bacteria in uveitis* Addison-Wesley, 1982 chapter 18. 465–88

Total hyphaema following streptokinase administration eight days after cataract extraction

SIR,—A 76-year-old man underwent an uneventful left sided extracapsular cataract extraction and intraocular lens (one piece, 7 mm) implantation under local anaesthesia. One day after surgery the visual acuity in the operated eye was 20/40 and improved to 20/25 with pinhole. Intraocular pressure was 12 mm Hg, and results of anterior and posterior segment examination were normal, except mild anterior uveitis. Neither hyphaema nor iris abnormalities were noted. The patient was treated with topical chloramphenicol 0·2% and dexamethasone phosphate four times a day. He had no systematic illness and did not take any other systemic or topical medication.

Eight days after surgery he was examined by us, four hours after the intravenous administration of 750 000 units of streptokinase for massive anterior wall myocardial infarction. The patient complained that vision in his left eye had deteriorated in the previous 30 minutes.

Examination revealed hyphaema in the anterior chamber of the left eye, reaching to about one-third of the anterior chamber's height and progressing in 20 minutes to total hyphaema, with reduction of visual acuity to hand movements only. The bleeding obscured the iris, lens, and posterior pole details. The intraocular pressure was 14 mm Hg, and extensive subconjunctival haemorrhage was also noted.

The visual acuity of the right eye was 20/70 owing to nuclear cataract. The intraocular pressure was 12 mm Hg, and anterior and posterior segments were normal.

The patient's medical treatment was not altered, and the macroscopic hyphaema resolved within the next 48 hours. Microscopic hyphaema was noted for another 48 hours. During that time intraocular pressure was between 12 and 15 mm Hg, and visual acuity gradually improved to 20/30.

Streptokinase is an enzyme that causes conversion of plasminogen to plasmin, which breaks up thrombi by cleaving fibrinogen. Intravenous administration of streptokinase is a standard and early treatment for patients with acute myocardial infarction; it improves survival and left ventricular function.[1]

We describe for the first time a case of total hyphaema, following administration of streptokinase in a patient eight days after an uneventful extracapsular cataract extraction and intraocular lens implantation. There was no other trauma to the eye, the patient was not treated with anticoagulants, and he did not undergo external cardiac massage. Furthermore a peripheral iridectomy was not performed during the operation. Thus we believe that the bleeding was caused by the streptokinase activity, and that surgery was probably the contributing factor. We cannot totally eliminate the possibility that the hyphaema might have been spontaneous.

Intraocular streptokinase has been used to treat experimental traumatic hyphaema, and it seems to shorten the time for its resolution.[2,3] Our patient had rapid resolution of the hyphaema within four days, indicating the possible action of streptokinase. We did not use antidotes like fresh frozen plasma, or ε-aminocaproic acid for two reasons: streptokinase activity may improve survival, and it also may help the hyphaema to resolve.

Our conclusion is that one has to be aware of the standard use of streptokinase in patients with myocardial infarction, as there is a possibility of intraocular bleeding in those patients who recently underwent intraocular surgery. Decisions on treatment with streptokinase should be taken without delay, since it may be life saving, and, if consulting with a cardiologist, our recommendation is not to defer treatment with it.

MICHAEL CAHANE
ISAAC ASHKENAZI
ISAAC AVNI
MICHAEL BLUMENTHAL
Goldschleger Eye Institute,
Chaim Sheba Medical Center,
Tel Hashomer Tel Aviv University,
Sackler School of Medicine, 52621 Israel

1 Verheugt FWA, Kupper AJF, Sterkmam LGW, Meijer A, Peels CH, Roos JP. Emergency room infusion of intravenous streptokinase in acute myocardial infarction: feasibility, safety, and hemodynamic consequences *Am Heart J* 1989; 117: 1018-22
2 Sinsky RM, Krichesky A. Experimental hyphema in rabbits, the effect of fibrinolytic enzymes on the rate of absorption. *Am J Ophthalmol* 1962, 54: 445–50.
3 Scheie HG, Ashley BJ, Burns DT Treatment of total hyphema with fibrinolysin *Arch Ophthalmol* 1963; 69: 147–53

BOOK REVIEWS

Textbook of Ophthalmic Plastic and Reconstructive Surgery. By Roger Kohn. (Pp 344; £65.30.) Lea and Febiger; Beckenham, Kent, 1988.

As its name implies, this is a textbook of ophthalmic plastic and reconstructive surgery, not a practical guide or manual. It has been written as a sequel to *Practical ophthalmic plastic and reconstructive surgery* by M J Reeh, C K Beyer, and G M Shannon, which was published in 1976. The author states that he wants the book to be comprehensive, and he is to be congratulated on having achieved this. The many excellent references ensure that, although the book is not encyclopaedic, every opportunity is provided for pursuing the subject further.

The usual subjects expected in a comprehensive textbook on oculoplastic surgery are discussed, such as anatomy, entropion, ectropion, ptosis, eyelid reconstruction, lacrimal, socket, orbital surgery, and fractures. In addition there are chapters devoted to basic principles of ophthalmic plastic surgery, congenital and craniofacial anomalies, and blepharospasm. The chapter on basic principles is particularly rewarding, including a discussion of wound healing, informed consent, skin preparation solutions, needles, suture materials, wound approximation, dog ears, flaps, and grafts. It is extremely useful to have insight into the principles of craniofacial surgery in a textbook which manages to remain so compact and to have a chapter devoted to the management of blepharospasm with a description of the alternatives of seventh nerve avulsion, orbicularis excision, and botulinum toxin injections.

Although the book is described as the sequel to *Practical ophthalmic plastic and reconstructive surgery*, it is in no way a new edition and is only the sequel because it is produced by the same publisher, with a 'foreword' by the two surviving authors of its predecessor. It is written very much by one author, ably helped by guest chapters on craniofacial abnormalities and orbital tumours, and reflects the author's personal approach to various problems which are not always those most used at present in ophthalmic plastic surgery, such as the two-pedicle tarsal rotation flap technique for treating lid retraction. He clearly does not like cryotherapy for the management of adnexal tumours, and it is not even mentioned when discussing carcinoma in situ, Bowen's disease, at the limbus. In other areas such as medial canthoplasty in the blepharophimosis syndrome both the more recognised and the author's individual techniques are described.

In summary, this is an excellent comprehensive textbook reflecting the author's personal approach to ophthalmic plastic surgery. It has been produced to a very high standard, with good drawings that have been photographed rather than the simpler line diagrams of its predecessor. It is written in a logical way, with each subject discussed in terms of its clinical presentation, differential diagnosis, surgical indications, operative techniques, and complications, and includes an extensive bibliography at the end of each chapter. As a textbook it should make a valuable addition for readers who are actively involved in ophthalmic plastic surgery.

J R O COLLIN

Manual of Oculoplastic Surgery. Edited by Mark R Levine. (Pp 268. £32.50.) Churchill Livingstone: Edinburgh, 1988.

This multiauthor book is part of Churchill Livingstone's 'Manuals in ophthalmology' series. In the preface the editor states that it is designed as a concise guide for performing many basic surgical procedures, and it assumes that the reader is well versed in the diagnosis and surgical indications associated with these various procedures The problem with any multiauthor book is the variable quality of the different contributions, but despite this it achieves remarkable consistency because of the format of each chapter, the artwork, and the grouping of the references under subject headings at the end of the book. This consistency is maintained by the fact that all the 42 contributors come from the USA with the exception of one each from Canada, Israel, and Korea. The book is written for practice in North America and is not aimed at the rest of the world. This is reflected in the early inclusion of chapters on cosmetic belpharoplasty and brow lifts and the absence of any section on such a common worldwide blinding condition as upper lid entropion.

The topics covered include anatomy, anaesthesia, trauma, cosmetic surgery, ptosis, lid retraction, entropion, ectropion, trichiasis, lid reconstruction, enucleation, evisceration, and socket, lacrimal, and orbital surgery. The individual procedures are well described and illustrated, and some of the indications for the operations are given in the opening sections of each chapter under 'goals and principles.' However, much is omitted For instance, there is no discussion in ptosis about the value of cutting the levator muscle in the management of Marcus Gunn jaw winking ptosis or aberrant third nerve regeneration or of unilateral versus bilateral ptosis surgery. There is no discussion on tumour management with radiotherapy, cryotherapy, or the laissezfaire technique. There must be concessions to limited space in any small book, and much is included which is excellent – for instance, the chapters on orbital surgery and trichiasis and the inclusion of a chapter on temporal artery biopsy and applied anaesthesia.

In summary, this book achieves its stated aim of describing a variety of current ophthalmic plastic surgical procedures. These are valuable if the reader surgeon is truly well versed in the diagnosis, medical treatment, and surgical indications for these procedures, as the editor supposes, provided he also has some knowledge of their limitations and alternatives.

J R O COLLIN

The Cornea. Eds Herbert E Kaufman, Bruce A Barron, Marguerite B McDonald, Stephen R Waltman. Pp 952. £140. Churchill Livingstone: London, 1988.

The editors of this book aim to provide a comprehensive understanding of the aetiology and course of corneal disease as well as an integrated approach to its medical and surgical management In addition they have edited each chapter to provide a cohesive consensus approach rather than a compendium of different authors' ideas. It is an excellent source of references and reviews on many subjects by many notable authorities and should be on the shelves of all libraries. However, the editors' ideals have been more succinctly achieved in other texts of lesser dimensions, and it would not therefore be my own choice as a sole work on this subject for an ophthalmologist with a special interest in the cornea.

The book is divided into a short introductory basic science section of 125 pages, and then the remainder is devoted to clinical matters. The chapter headings and layout are extensive and include an important section on the lids and tear film that are integral to understanding corneal disorders The colour plates are gathered together in three sections and are of variable quality in what is an otherwise well produced book.

The basic science chapters vary from an excellent summary of corneal structure and function to a rather disjointed survey of ocular inflammation and basic ocular immunology which, though clear, adds nothing to numerous similar reviews already widely available.

The clinical chapters vary in the extent to which they have achieved their aims. The problems with the co-ordination of the aims of the editors can be seen in several places. The chapter on the surgical management of eyelid abnormalities is confused in the classification of trichiasis and distichiasis, and, although the principles of surgical correction are clearly discussed, there is not enough detail for this to serve as an alternative to a surgical manual. This also applies to an otherwise excellent chapter on lamellar keratoplasty later in the book. The bacterial conjunctivitis section does not deal with the treatment regimens and frequency, though these are often poorly managed in clinical practice. The chapter on parasitic infections is unusual in a modern text for dealing well with a wide range of rare disorders. The chapters on congenital and metabolic disorders of the cornea are well laid out, making use of tables for comparison of the different disorders, whereas the same cannot be said of the chapter on epithelial and stromal disorders, which though compendious, leaves its subject as confused as ever. The chapter on pterygium is clear but, like those on epikeratophakia, does not deal with the literature on the results of the various techniques.

There are several lacunae that could have been avoided by tighter editorial control or a better choice of chapter headings. Minor omissions are the management of the corneal complications in the chapter on atopic diseases and the use of glue in the management of corneal perforations, which is hardly discussed. More important is the failure to discuss risk factors and success, in relation to graft survival, for penetrating keratoplasty despite a chapter being devoted to immunological considerations in corneal transplantation.

However, these criticisms stem partly from the high expectations excited by a text of this size and with so many expert contributors Much of the writing and content is of the highest quality. The remaining chapters are comprehensive and cover a wide field not usually found in standard texts. There are excellent chapters on neoplasms and trauma and a useful section on the management of corneal surface disorders. The chapters on the surgical management of postkeratoplasty astigmatism and radial keratotomy are particularly clear and contain a useful evaluation of results The editors are to be congratulated on assembling this book, which is a valuable resource for this important subject

J K G DART

NOTES

Ocular trauma

The 2nd International Symposium on Ocular Trauma will take place in Geneva, Switzerland, on 2–5 April 1992 The symposium is under the auspices of the International Society of Ocular Trauma (ISOT). Further information from KENES, Conference Organisers, PO Box 50006, Tel Aviv 61500, Israel.

Myopia

An International Congress on Myopia will be held on 17–20 September 1990 at the Plaza Hotel, Buenos Aires, Argentina. Further information from the Secretariat of the Congress, Av Pte. Sáenz Peña 720 5°A, (1035) Buenos Aires, Argentina.

Leonhard Klein Prize

The prize for 1991 will be awarded for work either already completed or in an advanced state of completion which contributes to science and research in ophthalmic surgery. The prize is 30 000 West German marks. The recipient is required to use it for further research in eye surgery. The composition of the Foundation Committee which will decide the awarding of the prize has been designated by the Council of the German Ophthalmological Society. The committee's decision is final. Recommendations from a third party are possible. The work should be submitted before 1 March 1991 in the German language to the Kuratorium der Leonhard Klein Stiftung, c/o Stifterverband für die Deutsche Wissenschaft e.V. zu Hd. Frau Ute Berkel, Postfach 23 03 60, 4300 Essen 1, Federal Republic of Germany.

AJO

AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 00029394 June 1990 Series 3, Vol. 109, No. 6

TABLE OF CONTENTS

ORIGINAL ARTICLES

Variable genotype of Leber's hereditary optic neuropathy patients Marie T. Lott, Alexander S Voljavec, and Douglas C Wallace

Septo-optic dysplasia in two siblings Jeffrey D. Benner, Mark W. Preslan, Edward Gratz, John Joslyn, Marcia Schwartz, and Shalom Kelman

Observations concerning patients with suspected impending macular holes J. Donald M. Gass and Brian C. Joondeph

Comparison of xenon arc and argon laser photocoagulation in the treatment of choroidal melanomas Jerry A. Shields, Lou C. Glazer, William F. Mieler, Carol L. Shields, and Mark S. Gottlieb

Bilateral choroidal osteoma in three siblings Kenneth G. Noble

Risk factors for postvitrectomy fibrin formation Glenn J. Jaffe, Daniel Schwartz, Dennis P Han, Mark Gottlieb, Arthur Hartz, Daniel McCarty, William F Mieler, and Gary W. Abrams

Spontaneous involution of subfoveal neovascularization Peter A Campochiaro, Kirk M. Morgan, Brian P. Conway, and John Stathos

Patterns of rod and cone dysfunction in Bardet-Biedl syndrome Samuel G. Jacobson, François-Xavier Borruat, and Peter P Apáthy

Indications for and outcomes of repeat penetrating keratoplasty Christopher J. Rapuano, Elisabeth J. Cohen, Steven E. Brady, Juan J. Arentsen, and Peter R. Laibson

HMB-45 antibody reactivity in pigmented lesions of the conjunctiva Ben J. Glasgow, Laurie C. McCall, and Robert Y. Foos

Collagen shield delivery of amphotericin B Steven D. Schwartz, Steven A. Harrison, Robert E Engstrom, Jr., Roger E. Bawdon, David A. Lee, and Bartly J. Mondino

Peribulbar anesthesia for strabismus surgery Reginald J. Sanders, Leonard B. Nelson, and James A. Deutsch

Limbal-based vs fornix-based conjunctival flaps in combined extracapsular cataract surgery and glaucoma filtering procedure J Franklin Murchison, Jr., and M. Bruce Shields

Evaluation of the Tono-Pen and the Pulsair tonometers Thomas A. Armstrong

Primate trabeculectomies with 5-fluorouracil collagen implants Ben Hasty, Dale K. Heuer, and Don S. Minckler

PERSPECTIVES

Mitochondria and Leber's hereditary optic neuropathy Nancy J. Newman and Douglas C. Wallace

LETTERS TO THE JOURNAL **CORRESPONDENCE** **BOOK REVIEWS**
ABSTRACTS **NEWS ITEMS**

The AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. © 1990, Ophthalmic Publishing Company. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

MICHAEL J. LUND
Subscription Correspondent

LINDA G. CLAUSEN
Records Manager

LAUREEN A. KOTT
Assistant to the Editor

LYNN ANN LINDVIG
Sales and Production

PATRICIA L. BERECK
Manuscript Editor

KAREN D. JOHNSON
Editorial Assistant

RENEE L. KASTAR
Assistant Media Planner

OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611, U.S.A.

Two new titles from the BMJ's series of books of general interest by medical writers

The MEMOIR Club

Not a Moment to Lose *by Sir David Smithers*

Sir David Smithers, former president of the British Institute of Radiology and of the Royal College of Radiologists, was for 30 years professor of radiotherapy at the Royal Marsden Hospital. But that is only half the story. He is also a man who believes that "one should aspire to be a realist but retain a sense of wonder, a rationalist who is prepared to jump to conclusions, and a critical visionary who remains sensible of the humour of the human situation". Recounting how he has lived according to these principles, David Smithers describes, in addition to his medical career, his experiences as a broadcaster, traveller, rose grower, and observer of human nature.

Inland £14.95; Abroad £17.50. BMA members: Inland £13.95; Abroad £16.50

One Man's Medicine *by Professor Archie Cochrane with Max Blythe*

Archie Cochrane was one of Britain's most influential thinkers on health care and the quality of health services. His 30 years' association with the Rhondda Fach—and his work there on reducing the suffering inflicted on whole communities by pneumoconiosis—is almost legendary. Ironically, this was nearly overshadowed later in his life by the spectacular success of his Rock Carling monograph *Effectiveness and Efficiency,* which proved to be a seminal work and influenced thinking about the assessment of medical treatment and procedures throughout the world.

What kind of man was he, and what led him to such a career? In *One Man's Medicine* (written in collaboration with Max Blythe) Archie Cochrane recalls with candour and perception the dilemmas and disasters that beset his early ambitions for a career in clinical medicine and research; his undergoing psychoanalysis with Theodor Reik in Germany in the early 1930s; his support for the republicans in Spain; and his four years as a prisoner of war in Salonica (for which he usually blamed Evelyn Waugh).

A rich and rewarding book, *One Man's Medicine* sums up the life and opinions of a remarkable man.

Inland £14.95; Abroad £19.00 BMA members: Inland £13.95; Abroad £18.00

Crown copyright
The x-ray service of the Medical Research Council's Pneumoconiosis Research Unit visiting Tylorstown pithead in 1950.

Together with the Nuffield Provincial Hospitals Trust, the BMJ has reprinted *Effectiveness and Efficiency.* This new edition also includes a brief note written by Archie Cochrane reflecting upon the monograph some two years after its publication, and the obituary written with such honesty by himself.

Inland £9.95; Abroad £12.50 BMA members: Inland £8.95; Abroad £11.50

ORDER FORM British Medical Journal, PO Box 295,
London WC1H 9TE, England *or any leading bookseller*

Please send me the following books:

The MEMOIR Club

☐ **Not a Moment to Lose**
☐ **One Man's Medicine**
☐ **Effectiveness and Efficiency**

Prices to include postage, by air abroad

NAME ....
Please print name and address clearly
ADDRESS ....
....
POST CODE ....

☐ I enclose .... BMA Membership No. ....

Please make cheques payable to British Medical Journal or debit my credit card (*please tick box*)

☐ VISA ☐ AMERICAN EXPRESS ☐ MASTERCARD

CARD NUMBER ______________________
Card expiry date ....
Signature ....

☐ Please send me a details of previous Memoir Club books

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- **24 hour delivery.**
- **Courier services.**
- **Personal delivery.**

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia

Advancing The New Biology

A brighter start for dry eyes...

begins last thing at night

Used at night Lacri-lube soothes, protects and lubricates dry eyes for undisturbed sleep and comfort on waking.

LACRI–LUBE®
petrolatum mineral oil **OINTMENT**

At the end of the day there's nothing quite like it for dry eyes

Lacri-Lube Prescribing Information. Presentation: Sterile, bland, non-medicated ophthalmic ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. **Uses:** Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. **Dosage and administration:** For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. **Contra-indications etc:** No known contra-indications. **Pharmaceutical precautions:** Store away from heat. To avoid contamination during use, do not touch tip to any surface. **Legal Category:** P. **Package quantities:** Available in 3.5g ophthalmic tubes. **Basic NHS Cost:** (as at May 1987) £1.76. **Product Licence Number:** PL 0426/0041. **Product Authorisation Number:** PA 148/38/1 (Allergan Pharmaceuticals (I) Limited, Westport, Co Mayo).

ALLERGAN PHARMACEUTICALS ™

SCIENCE WITH VISION

Allergan Limited.
High Wycombe, Bucks. HP12 3SH

Full prescribing information is available on request. ®denotes registered trademark

SEP 1990

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

449 Exfoliation syndrome *A Garner*

Original articles

450 Immunogold localisation of laminin in normal and exfoliative iris *A G Konstas, G E Marshall, W R Lee*

458 Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules *A P Watson, E S Rosen*

462 Artificial maintenance of the relative ocular tissue pressure during eye surgery *C Maggi, R Maggi*

465 Ocular and visual defects in a geographically defined population of 2-year-old children *Maureen Stayte, Ann Johnson, Catherine Wortham*

469 Conjunctival biopsy in the diagnosis of sarcoidosis *Richard F Spaide, David L Ward*

472 Changes in waveform of congenital nystagmus associated with biofeedback treatment *Mikako Mezawa, Satoshi Ishikawa, Kazuhiko Ukai*

477 A study of the causes of non-compliance by patients prescribed eyedrops *A J Winfield, D Jessiman, A Williams, L Esakowitz*

481 Extraocular muscle surgery for Graves' ophthalmopathy: does prior treatment influence surgical outcome? *Maarten Ph Mourits, Leo Koorneef, Ada M van Mourik-Noordenbos, Helma M van der Meulen-Schot, Mark F Prummel, Wilmar M Wiersinga, Arie Berghout*

484 Graves' ophthalmopathy: V. Aetiology of upper eyelid retraction in Graves' ophthalmopathy *Steven E Feldon, Lori Levin*

486 Stabilisation of refraction following extracapsular cataract extraction *P Baranyovits*

490 Incidence of inadvertent globe perforation during strabismus surgery *R J Morris, P H Rosen, P Fells*

Mini review

494 Neuro-ophthalmology *M D Sanders*

Case reports

496 Hemifacial atrophy: an unusual cause of enophthalmos *K N Hakin, C Yokoyama, J E Wright*

498 Vitreous haemorrhage as a complicaton of HELLP syndrome *Steven R Leff, David L Yarian, Leo Masciulli, Stuart N Green, Roy E Baldomero*

499 Optic nerve avulsion due to forced rotation of the globe by a snooker cue *P G Hykin, I D Gardner, S M Wheatcroft*

502 Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis *C Mark Antle, Karim F Damji, Valerie A White, Jack Rootman*

505 Aneurysmal bone cyst of the sphenoid with orbital involvement *Jill V Hunter, Cheryl Yokoyama, Ivan F Moseley, John E Wright*

509 Yellow forelock – a new neuro-ophthalmological sign *R I Kellen, B Schrank, R M Burde*

511 **Book review Letters to the editor**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE
Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Journal

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced.*

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof, and should read it carefully for printers' errors. Alterations to the original text should be kept to a minimum and may be charged to the author.

REPRINTS may be ordered from the Publishing Manager when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Ophthalmology*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not, however, required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents of the publication without prior permission is always illegal.

NOTICE TO ADVERTISERS Applications for advertisement space and for rates should be addressed to the Advertisement Manager, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *British Journal of Ophthalmology* is published monthly. The annual subscription rates are £106.00 inland and £126.00 overseas (US $200.00). Orders should be sent to the Subscription Manager, British Journal of Ophthalmology, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. All inquiries regarding air mail rates and single copies already published should be addressed to the Publisher in London.

Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR and
printed by
[illegible]ount Printing Co
Ltd, Hong Kong

NIGHT WORKER.

Alcon's Maxitrol Ointment has been developed to provide the same highly effective action against inflammation and infection as Maxitrol drops but with an added benefit.

It is ideal for overnight use.

Consequently, a patient's sleep need not be disturbed, whether in hospital or at home, because Maxitrol goes on working through the night.

MAXIMISE
ON
MAXITROL®

Dexamethasone/Polymyxin B Sulphate/Neomycin Sulphate

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford,
Herts. WD2 4YR.
Telephone: 0923 246133 Fax: 0923 245331

PRESCRIBING INFORMATION:

PRESENTATION: Dexamethasone Ph. Eur. 0.1% Polymyxin B Sulphate Ph. Eur. 6,000 units/g and Neomycin Sulphate Ph. Eur. equivalent to Neomycin 3.5mg/g in an ointment base. **CLINICAL USES:** Management of infectious ocular inflammations produced by organisms which are sensitive to Neomycin Sulphate and Polymyxin B Sulphate. Acute or chronic non-purulent conjunctivitis, blepharo-conjunctivitis, kerato-conjunctivitis, non-specific superficial keratitis, deep keratitis, and acne rosacea keratitis, herpes zoster ophthalmicus, iridocyclitis, mild acute iritis, recurrent marginal ulceration, corneal ulcer, non-purulent blepharitis, scleritis, episcleritis and sclero-conjunctivitis. Post-operatively to prevent ocular infection. **DOSAGE AND ADMINISTRATION:** Apply a small amount of ointment into the conjunctival sac, 3-6 times a day. When a favourable response is observed, the dosage may be reduced to 3-4 applications per day. This may be followed by once a day applications for several more days. **CONTRA-INDICATIONS:** This drug is contra-indicated in tuberculous, fungal and most viral lesions of the eye (herpes simplex/dendritic keratitis), vaccinia, varicella; acute purulent conjunctivitis and acute purulent blepharitis; and in those persons who have shown hypersensitivity to any of its components. **WARNINGS:** Extended use of topical therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If the condition does not respond within a reasonable period other forms of therapy should be instituted. Appropriate measures should be taken when this occurs. A few individuals may be sensitive to one or more components of this product. If any reactions indicating sensitivity are observed discontinue use. Extended use of topical steroids is a possible factor in the formation of subcapsular cataracts. **PREGNANCY WARNING:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long term treatment of pregnant patients. **LEGAL CATEGORY:** POM. **PACKAGE QUANTITY** 3.5g. **PRODUCT LICENCE NO:** 0649/5916.

USED TO TREAT
OVER 2 MILLION
PATIENTS

USED IN 153
COUNTRIES

OVER 1,000
CLINICAL PAPERS
PUBLISHED

WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children. *Nursing:* Mother should either stop nursing or stop 'Timoptol'. *Pregnancy:* Not studied; weigh benefit against possible hazards.

SIDE EFFECTS

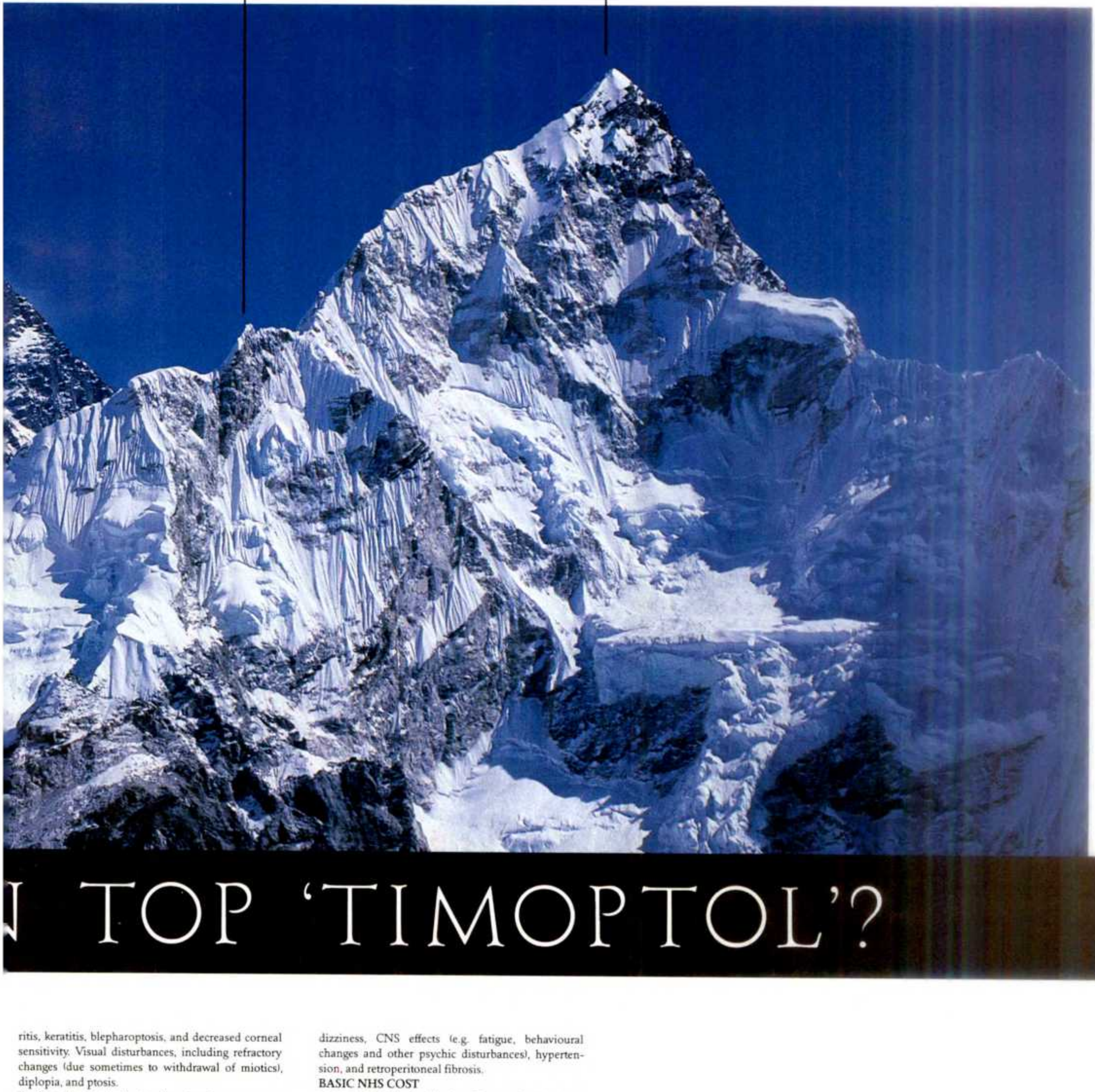
Ocular irritation, including conjunctivitis, blepha-

12-90 TOT.89.GB.4697.J

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
OPEN-ANGLE GLAUCOMA
HERAPY BY THE MAJORITY
F UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE



TOP ‘TIMOPTOL’?

ritis, keratitis, blepharoptosis, and decreased corneal sensitivity. Visual disturbances, including refractory changes (due sometimes to withdrawal of miotics), diplopia, and ptosis.

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest.

Bronchospasm (predominantly with pre-existing bronchospastic disease), respiratory failure, dyspnoea.

Headache, asthenia, nausea, dizziness, depression.

Hypersensitivity, rash, and urticaria.

Reactions with an unestablished relationship are ACMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST

0.25% Ophthalmic Solution ‘Timoptol’, £5.18 per 5 ml pack. 0.5% Ophthalmic Solution ‘Timoptol’, £5.82 per 5 ml pack.

Product licence numbers:

0.25% Ophthalmic Solution ‘Timoptol’, 0025/0134.
0.5% Ophthalmic Solution ‘Timoptol’, 0025/0135.

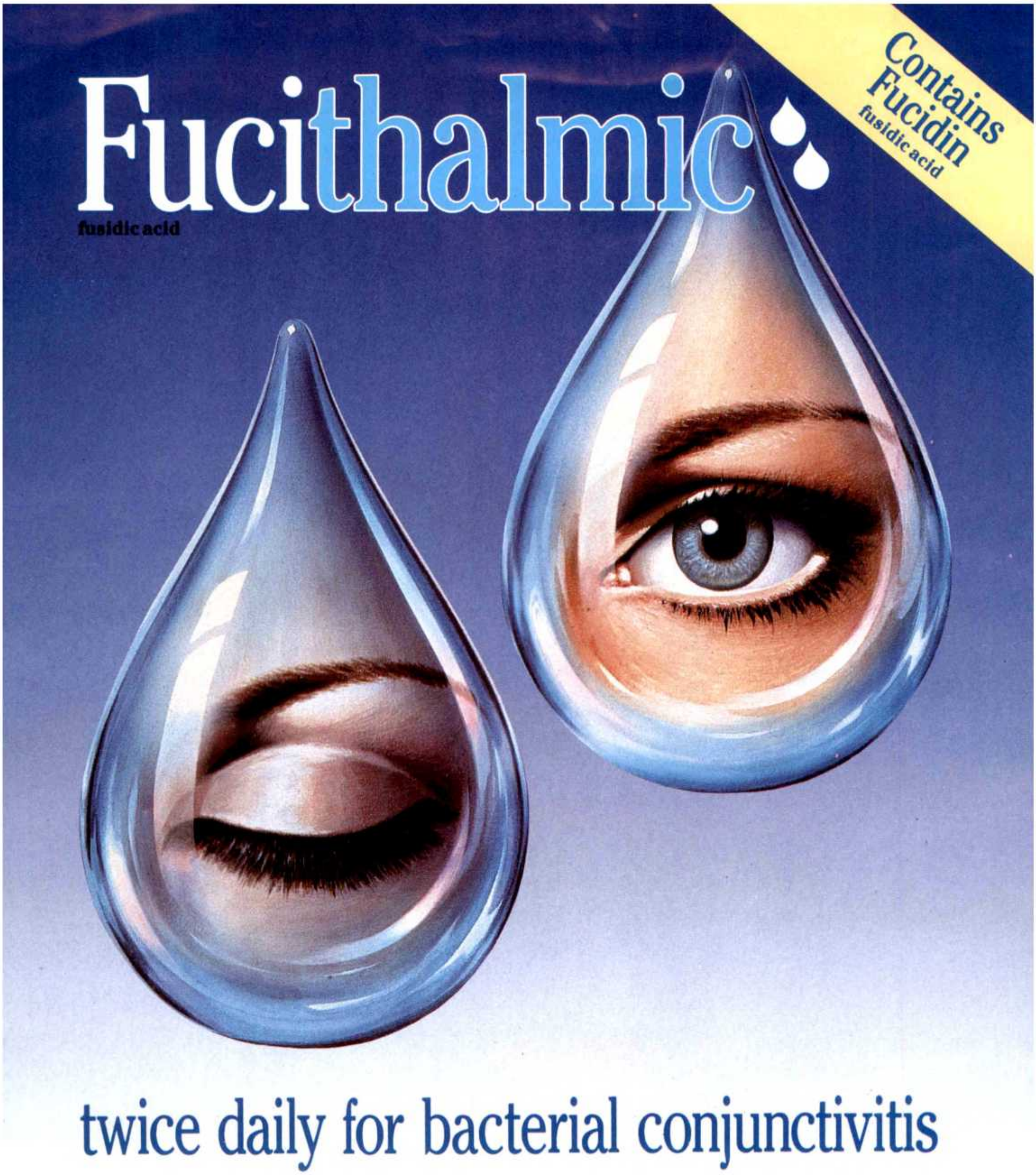
® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference

1. Data on file, Merck Sharp & Dohme Limited.

Ophthalmic Solution
Timoptol®
(timolol maleate, MSD)

UNSURPASSED AS FIRST-LINE GLAUCOMA THERAPY


Fucithalmic
fusidic acid
Contains Fucidin fusidic acid
twice daily for bacterial conjunctivitis

▼ Prescribing Information.

Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses:** Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications:** Bacterial conjunctivitis due to sensitive organisms. **Dosage:** One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications:** Hypersensitivity to any component. **Precautions:** Should not be used when contact lenses are being worn. **Side effects:** Transient stinging. Hypersensitivity may occur. **Product Licence Number:** 0043/0137. **Basic N.H.S. Price:** £2.25/5g tube.

LEO

Further information available on request:

Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

Exfoliation syndrome

In 1917 Lindberg,[1] a Finnish ophthalmologist, gave the first published description of a condition that for a time was known as exfoliation of the anterior lens capsule. Associated with a risk of spontaneous lens displacement, posterior synechiae, and a high level of glaucoma such that about 50% of patients are likely to be affected, the disorder has been shown to have a worldwide prevalence and age-related incidence. Subsequent observers considered that the material accumulating on the lens surface originated elsewhere in the eye, though where that might be was obscure, and the term pseudoexfoliation of the lens capsule came to be preferred. Nowadays, however, because there is evidence of multifocal deposition and, possibly, origin, a cautious retreat to the simple designation exfoliation syndrome is gaining in popularity.

The notion that the abnormal substance observed on the front of the lens and elsewhere in the anterior segment might represent true capsular material is readily dismissed, since, unlike the capsule, which is essentially collagenous, the exfoliation deposits are resistant to collagenase digestion and include almost no hydroxyproline. On the other hand the possibility that they are an alternative product of the lens epithelium has not been ruled out. Thus fibrillar material morphologically indistinguishable from that seen on the lens surface in affected patients can be found beneath the capsule in the anterior equatorial region, sometimes apparently arising from small pits in the underlying epithelium.

We would be in a better position to determine the source of exfoliation material if only we understood its nature. Electron microscopy demonstrates a loose fibrillar structure, with individual fibrils being generally 20–30 nm thick and having a characteristic 50 nm macroperiodicity. On the basis of its ultrastructural appearance, specific histochemical staining reactions, and an affinity for antibody to fibrillin it has been suggested that the disorder is one involving the microfibrillar component of elastic tissue. Of relevance is the fact that the lens zonules have a similar ultrastructural, staining, and immunological properties, which could mean that the exfoliation material represents an overproduction of zonular tissue on the part of the non-pigmented ciliary epithelium and perhaps the equatorial lens epithelium. There are, however, some differences in amino acid composition between the two structures.

Moreover, there is also compelling evidence for the presence of other components which include glycosaminoglycans and non-collagenous basement membrane protein. A claim that amyloid protein, other than a plasma derived moiety, is implicated is not well substantiated. That the syndrome is primarily a disorder of basement membrane metabolism originated with the finding by electron microscopy of exfoliative material adjacent to the various epithelial tissues of the anterior segment and blood vessels of the iris, though it was hinted at as early as 1929 by Trantas,[2] who alluded to involvement of the so-called 'glass membranes.' Deposits have also been observed in the conjunctiva, raising the possibility that the disorder is more than a purely local phenomenon. Now in this issue of the *BJO* Drs Konstas, Marshall, and Lee present evidence showing that the non-collagenous protein laminin is a major constituent of the untoward basement membrane derived material. This particular protein is a complex molecule which helps to hold the membrane together and promote adhesion and regeneration of the overlying cells. The authors also indicate that, in the context of the iris vasculature, pericytes and smooth muscle cells are the probable source of the exfoliated laminin, though it is to be noted that many cell types, including the epithelial layers of the iris, ciliary body, and lens, are associated with similar activity.

So what are we to conclude? If, as now seems probable, the exfoliated material includes, among other things, both the fibrillar component of elastic tissue and the principal non-collagenous component of basement membranes, it is reasonable to suppose that a disturbance of an as yet unknown factor controlling specific aspects of extracellular matrix metabolism is a fundamental issue. Furthermore, since the incidence of the syndrome increases with age, it may be that external influences are concerned in the propagation of the disturbance.

A GARNER

1 Lindberg JG Kliniska undersokningar over depigmenteringen av pupillarranden och genomlysbarheten av iris vid fall av ålderstarr samt i normala ogon hos gamla personer. Dissertation, Helsingfors, 1917.

2 Trantas A. Lésions séniles de la capsule antérieure du cristallin et du bord pupillaire *Arch Ophtalmol (Paris)* 1929; 46: 482–91

British Journal of Ophthalmology, 1990, 74, 450–457

ORIGINAL ARTICLES

Immunogold localisation of laminin in normal and exfoliative iris

A G Konstas, G E Marshall, W R Lee

University of Glasgow, Western Infirmary, Glasgow Department of Ophthalmology
A G Konstas

Department of Pathology
G E Marshall
W R Lee

Correspondence to:
Dr A G Konstas, Department of Ophthalmology, University of Glasgow, Western Infirmary, Glasgow G11 6NT.

Accepted for publication
29 March 1990

Abstract

Immunoelectron microscopic studies of exfoliative iris tissue (seven specimens) revealed the presence of laminin in the fibrillar component of exfoliation material. The immunogold label was uniformly distributed on the exfoliation fibres. Deposition of laminin labelled exfoliation material in the dilator muscle was a noteworthy feature, as was an apparent depletion of laminin in the basement membranes of ostensibly unaffected vessels. In control iris tissue (five enucleated eyes) laminin was identified in the basement membrane round vascular contractile cells, but not beneath the endothelium.

Exfoliation syndrome, alternatively referred to as pseudoexfoliation syndrome, is an intriguing age-related ocular disorder characterised by the production and deposition of an abnormal protein in the anterior segment of the eye. The disease is of major clinical significance, since it is intimately associated with glaucoma.[1 2] Intensive studies have not yet revealed the precise nature of the exfoliation material.

TABLE I *Clinical details: normal iris cases*

Case no	*Age*	*Sex*	*Indication for enucleation*
1	28	M	Choroidal melanoma
2	63	F	Choroidal melanoma
3	65	M	Choroidal melanoma
4	69	M	Choroidal melanoma
5	81	F	Secondary glaucoma

TABLE II *Clinical summary of patients with exfoliation*

Case no	*Age*	*Sex*	*Clinical presentation*	*Other clinical findings*	*Indication for surgery*
1	82	M	Exf syndrome Normal IOP C/D ratio=0 5	Iridodonesis Partial lens subluxation	Cataract extraction
2	69	M	Exf glaucoma IOP=32 mmHg VF loss stage I C/D ratio=0·6	Iris pigm Angle Pigm 3+ SPL	Failed medical Rx
3	79	F	Exf glaucoma IOP=34 mmHg VF loss stage II C/D ratio=0·6	Angle pigm 3+ SPL	Failed medical Rx
4	69	M	Exf glaucoma IOP=24 mmHg VF loss stage III C/D ratio=0·6	Corneal pigm Angle pigm 3+ SPL	Failed medical Rx
5	75	M	Exf glaucoma IOP=50 mmHg VF loss stage III C/D ratio=0·6	Iridodonesis Angle pigm 4+ SPL	Poor compliance
6	68	M	Exf glaucoma IOP=50 mmHg VF loss stage IV C/D ratio=0·7	RAPD Angle pigm 2+	Early trabeculectomy
7	65	M	Exf glaucoma IOP=34 mmHg VF loss stage IV C/D ratio=0·8	Exf on cornea Iris pigm Angle pigm 3+ Phakodonesis	Early trabeculectomy

Exf=exfoliation. VF=visual field C/D=cup to disc. Pigm=pigmentation SPL=Sampaolesi's line present. RAPD=relative afferent pupillary defect. Rx=treatment.

By light microscopy the appearance and distribution of exfoliation material are well documented. In brief, eosinophilic clumps of bush-like material are deposited on the ciliary processes, the zonular fibres, the surfaces of the lens, and the iris, and within the trabecular meshwork and stroma of the conjunctiva.[3] Electron microscopy shows exfoliation material to consist of fibres formed from filamentous subunits, with a varied periodicity (17–56nm) and embedded in an interfibrillar matrix.[3 4] It is generally accepted that exfoliation material is composed of a variety of biochemical constituents.[5] Histochemical staining was obtained for proteoglycans[6] and glycoproteins,[7] and similarities were shown between exfoliation material and the ocular zonular fibres,[8] oxytalan,[9] and constitutents of the elastic system.[10-12]

It has long been speculated that the material may be abnormal basement membrane synthesised at multiple sites by defective aging cells.[13] Since basement membranes contain collagenous and non-collagenous components, disordered synthesis or degradation of non-collagenous components may be a significant feature of the disorder.[14]

In normal tissue one non-collagenous component, namely laminin, has been identified by established immunocytochemical techniques.[15 16] We therefore decided to investigate the presence of laminin in exfoliation material. Exfoliative iris tissue was used in this study on account of the early involvement of the iris in the disease process[17] and the great abundance of exfoliation material present therein.[18] As laminin distribution has not been described in the normal iris, we included an examination of an adequate sample of normal iris tissue as an integral part of this investigation.

Patients and methods

Normal iris tissue was obtained from freshly enucleated eyes of four patients suffering from choroidal melanoma and one patient with absolute glaucoma (Table I). Representative blocks were dissected from the peripheral part of the iris, and control tissue for laminin was taken from the central part of the cornea. The iris specimens were ostensibly normal on microscopic examination of toluidine blue stained LR white (London resin white) semithin sections.

Exfoliative iris tissue was obtained from seven peripheral iridectomies performed during six trabeculectomies and one intracapsular cataract extraction. Table II provides the clinical details of these patients. The visual field loss was graded from I to V stages by the classification described by Jay and Murray.[19] Five of the patients were examined by one of us (AGK) before the operation. The other two patients had been examined by their ophthalmologist in a sister hospital. All the surgical specimens were processed in an identical manner.

FIXATION AND PLASTIC EMBEDDING

The specimens were immersed immediately after enucleation or iridectomy in a freshly made fixative solution of 4% paraformaldehyde plus 0–1% glutaraldehyde in 0·1 M Sörensen's phosphate buffer or cacodylate buffer at pH 7·2. After 10 minutes the enucleated eyes were opened to allow for rapid penetration of the fixative into the globe. Fixation was continued for two hours at room temperature. After fixation the blocks were washed three times in buffer (5 min) and processed for LR white embedding, the details of which have been described.[20]

ANTIBODIES

Polyvalent rabbit antibodies against laminin were supplied by Heyl (Berlin, West Germany) and had been raised in rabbits by multiple injections of human laminin. The serum was tested by the supplier with the following immunological assays: ELISA, immunoblot, and immunohistology (fluorescence, APAAP).

IMMUNOCYTOCHEMISTRY

Ultrathin sections (silver-gold) were cut on an LKB Ultrotome Nova (Cambridge Instruments), mounted on 200 mesh nickel grids, and left to dry for 10 minutes before rehydrating on drops of distilled water. The antibody dilutions in trometamol (Tris) buffer plus 1% bovine serum albumin (BSA), determined by previous experimental work, were 1:20–1:40. Incubation with the laminin primary antibody was performed at room temperature for two hours. Immunogold labelling was performed with a 1:40 dilution of goat anti-rabbit gold conjugate (10 nm), which was supplied by Biocell Laboratories, Reading, UK. The precise immunocytochemical procedure is described elsewhere.[15 20]

CONTROLS

Normal rabbit serum negative controls (Sigma) were concurrently conducted at the same dilutions. Omission of the primary antibody was also used as a negative control. Human cornea, fixed in 4% paraformaldehyde for two hours and processed in an identical manner to the iris specimens examined, was used as a positive control for laminin.[15]

Results

NORMAL IRIS

In all five iris specimens laminin was specifically localised to the basement membranes within the walls of blood vessels and to the extracellular matrix in the dilator muscle region. The specific features are as follows:

Vasculature. The label was most intense on the matrix surrounding the myocytes of the larger iris vessels (Fig 1A). Labelling for laminin was prominent in large and medium sized vessels and greatly reduced or absent in small vessels. When present in small vessels, immunolabelling was seen to be more intense on the outer side of pericytes. Of the five cases studied the highest intensity of labelling around small vessels was observed in the youngest individual (see Table I): in this particular specimen laminin was demonstrated throughout the whole of the iris vasculature. In contrast, laminin was markedly reduced in iris vessels from the oldest patient.

Pigment epithelium. Laminin was localised to the extracellular matrix in which the basal muscular portion of the anterior iris pigment epithelium was embedded (Fig 1B). Immunolabelling was mainly concentrated on dense bands of filaments within an amorphous granular substance filling the intercellular spaces. Labelling intensity increased in proportion to the quantity and density of the filamentous bands and was mainly restricted to those electron dense areas in all normal iris specimens studied. Laminin was also demonstrated on the basement membrane of the anterior iris pigment epithelium. The thin basal membrane of the posterior pigment epithelium of the iris showed weak but specific labelling.

Of particular interest was the strong signal associated with iris fibrocytes which form the boundary between the dilator muscle region and iris stroma. Labelling was intense on filamentous bodies adjacent to these fibrocytes (Fig 1C). Among the five normal iris specimens studied the highest density of immunogold particles in the dilator muscle region was in the youngest patient.

Stroma and anterior border layer. Gold particles were absent from the iris stroma and associated cells (fibrocytes, melanocytes, and mast cells). However, a discrete localised label was present on small clusters of filaments associated with multilayered fibrocytes of the anterior border layer. Such labelling was generally absent from the outermost layer of fibrocytes.

EXFOLIATIVE IRIS

Exfoliation material. Intense labelling for laminin was observed over areas where exfoliation material was present within the iris. This finding was consistent in all seven exfoliative iris cases. Labelling was regarded as extremely specific on the basis of the absence of gold particles from the nuclei, cell cytoplasm, and lumina of blood vessels. Better antigenic preservation was

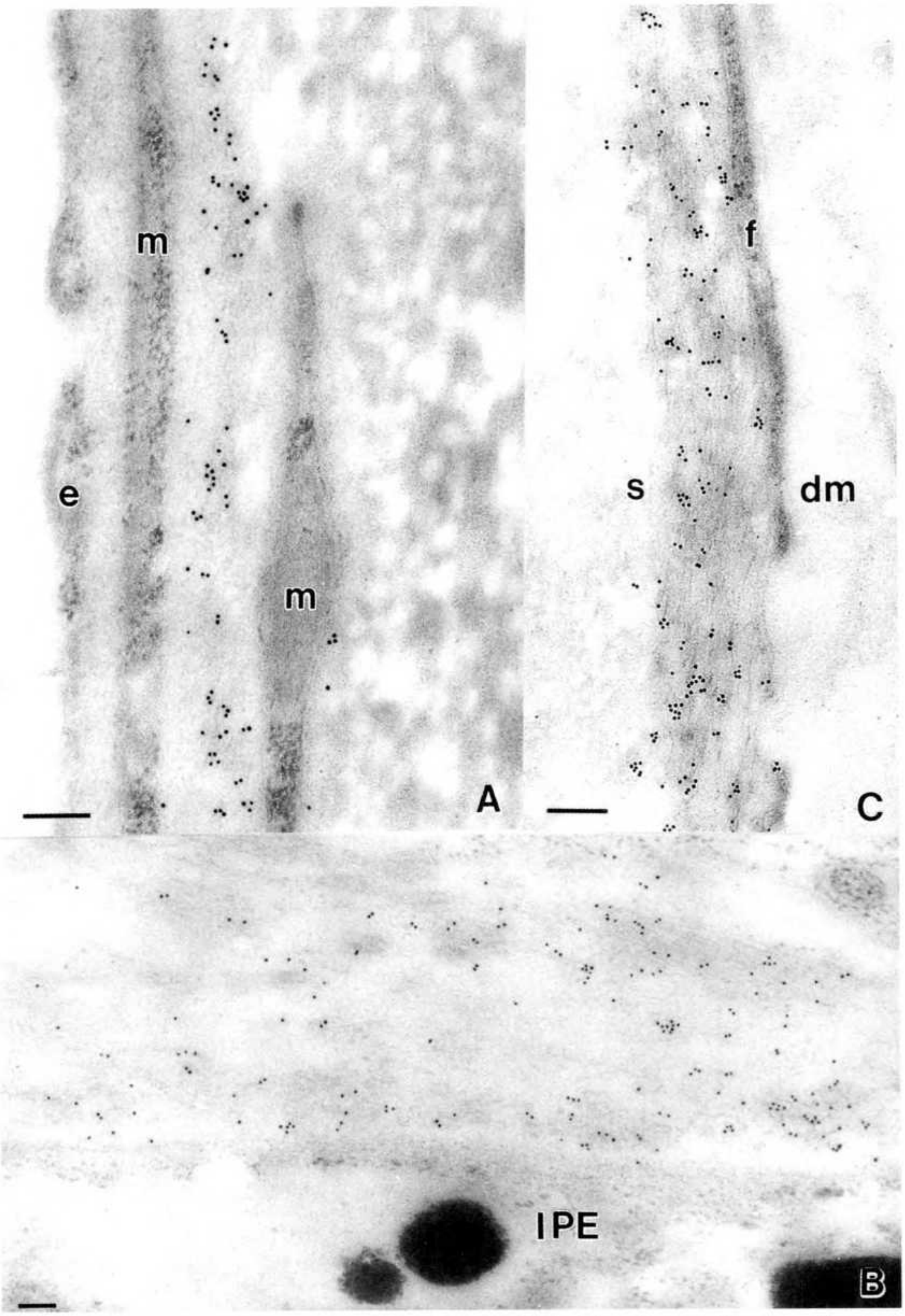


Figure 1: Labelling for laminin in the extracellular matrix of the normal iris. A: In the wall of a vessel there is a positive signal in the fibrillar matrix between two myocytes (m), but not in the basement membrane of the endothelium (e). B: In the matrix anterior to the anterior iris pigment epithelium (IPE) laminin is localised to the clumps of filamentous electron dense material. C: The parallel filamentous bundles adjacent to the stromal fibrocytes (f) exhibit a strong signal for laminin. (dm): Dilator muscle region. (s): Iris stroma. (Bar=200 nm.)

achieved in formaldehyde fixed tissue, but this was at some expense of ultrastructural preservation. In glutaraldehyde fixed tissue immunolabelling was less intense but highly specific. Recognition of the exfoliation material was relatively easy in LR white processed tissue. This was due to a difference in tissue contrast in comparison with conventionally processed tissue, which resulted in greater detail in the extracellular matrix components. In addition it was found that larger amounts of extracellular matrix material were retained with the LR White embedding procedure. Laminin was present predominantly in the exfoliation fibres, but weak labelling was also observed on the electron-lucent interfibrillar matrix (Fig 2A, B).

In four of the cases, vegetations consisting of laminin labelled exfoliation material were seen to project into the anterior chamber from the anterior border layer (Fig 2A). Within an

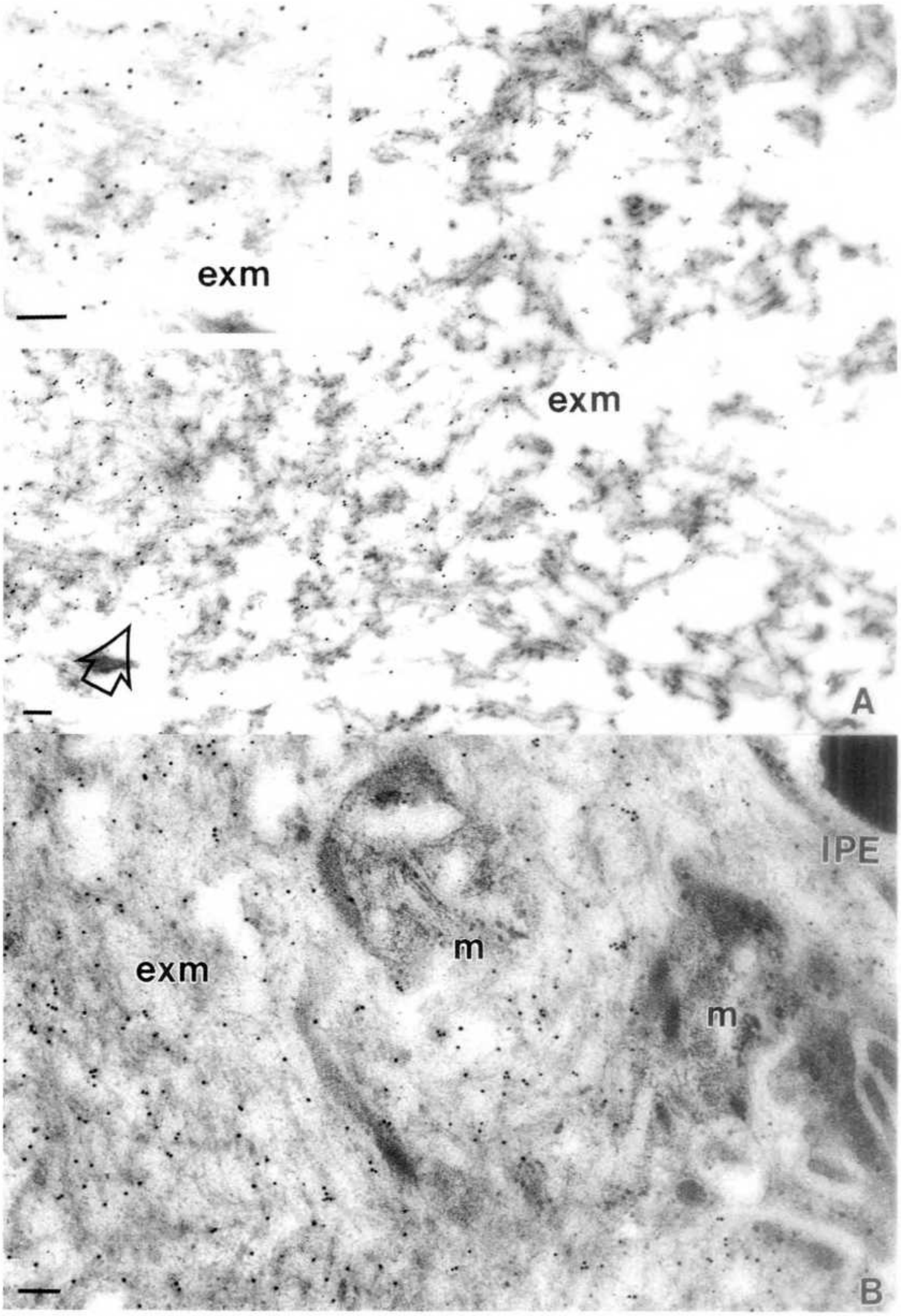


Figure 2: A: Positive laminin labelling in the loosely arranged exfoliation material (exm) in a vegetation on the anterior iris surface. The labelling is predominantly on the fibrillar component (see inset for high magnification of area marked with an arrow). A similar labelling pattern is seen in the more compact band of exfoliation material adjacent to the iris pigment epithelium (IPE) and around the processes of the dilator muscle (m). (Bar=200 nm.)

individual case the intensity of immunogold localisation was proportional to the density of the exfoliative deposits. The highest labelling intensity was observed on dense deposits in the dilator muscle region (Fig 2B) and round large iris vessels.

Vasculature. In the exfoliative iris the walls of some blood vessels were found to be free from deposits of exfoliation material. Rather surprisingly, in such exfoliation-free vessels, basement membrane labelling for laminin was markedly reduced or absent in comparison with normal iris vessels.

In exfoliative vessels (that is, vessels associated with exfoliation material) immunolabelling was predominantly localised to the exfoliation material (Fig 3A, B, C). In all vessels in which clumps of exfoliation material were observed a thin label-free zone was noted corresponding to the lamina lucida of endothelial cell basement

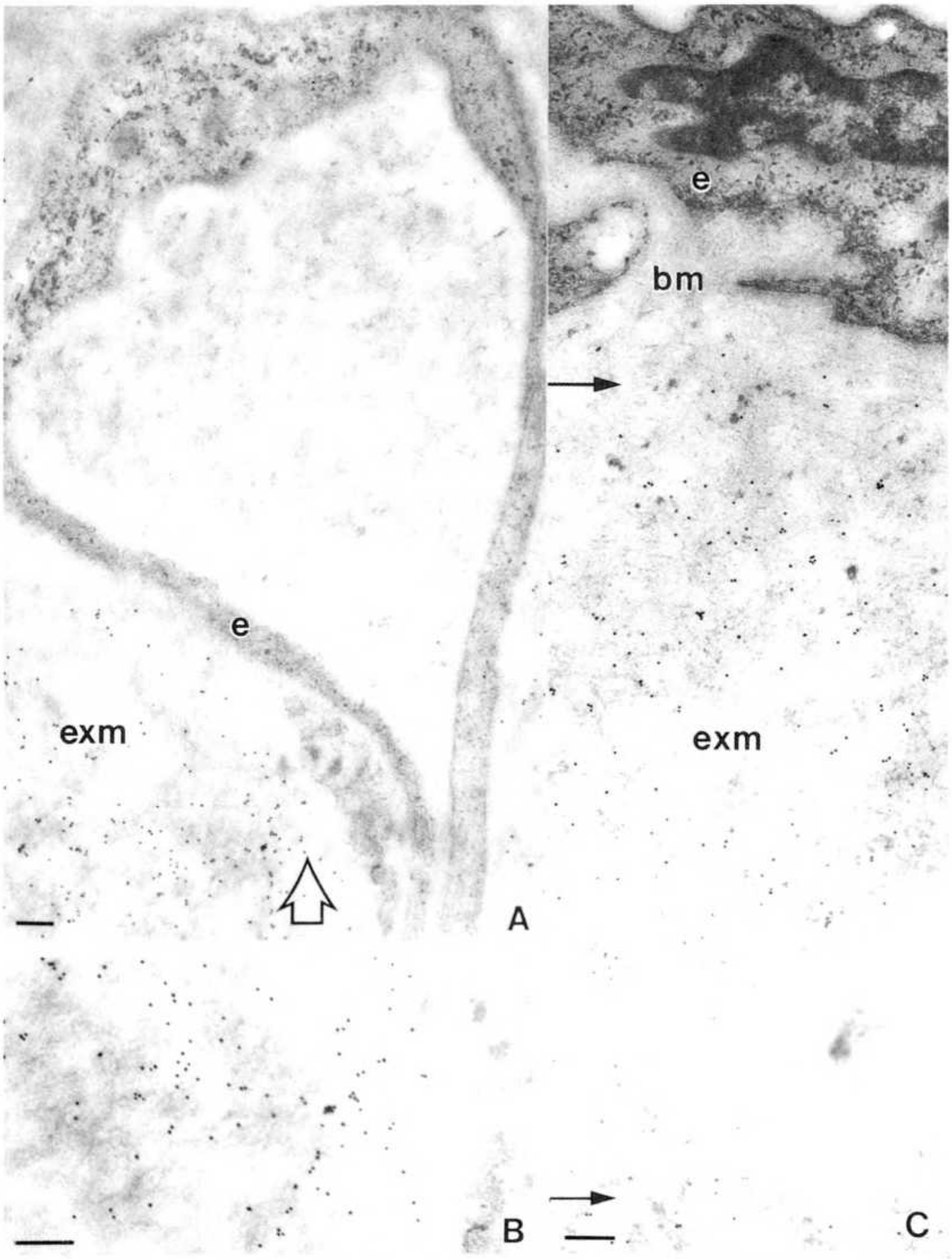


Figure 3: Exfoliation material labelled with laminin in the walls of iris vessels. A: The endothelium (e) appears atrophic and the exfoliation material (exm) had a poorly defined fibrillar component because the fixative was glutaraldehyde-free. B: The area marked with an arrow is shown at high magnification. C: The total extent (between arrows) of the exfoliation material (exm) deposition around a vessel is shown; glutaraldehyde in the fixative intensifies the fibrillar component. Note the absence of immunolabelling from the basement membrane (bm) of the endothelium (e). (Bar=200 nm.)

membrane. The adjacent lamina densa was often obscured by exfoliation material, which was strongly labelled for laminin (Fig 3). The clumps of exfoliation material often extended from within the walls of the iris vessels into the iris stroma. In many of the exfoliative vessels containing exfoliation material the endothelial cells were attenuated and the myocytes were atrophic (Fig 3A). This was particularly evident in advanced cases of exfoliation glaucoma.

Pigment epithelium. We were intrigued with the association between exfoliation material and the dilator muscle (Fig 2B). In four of the specimens exfoliation material had infiltrated the basal muscular portion of the anterior iris pigment epithelium, causing a marked disturbance in the architecture of this layer. Laminin was again mainly localised in the exfoliation fibres. In case 7, where exfoliation material had infiltrated wide areas of the dilator muscle region (Fig 2B), laminin labelling on the deposits was intense. Exfoliation material frequently surrounded the muscular processes of the anterior iris pigment epithelium and was observed between the intact walls of epithelial cells, but did not penetrate the cell membrane. In no specimen was exfoliation material noted between the two layers of the pigment epithelium, nor was it seen on the basal

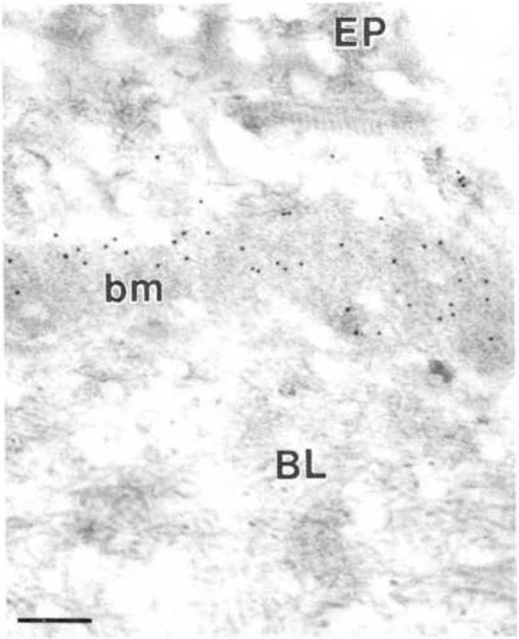


Figure 4: Example of positive corneal control. Laminin is localised in the basement membrane (bm) beneath the epithelium (EP) of the cornea. Note the absence of labelling in Bowman's layer (BL) (Bar=200 nm.)

surface of the posterior layer of the pigment epithelium. The latter finding may have been due to the loss of exfoliation material during surgical handling of the tissue.

With regard to the positive corneal control employed in this study, laminin was demonstrated in the basement membrane of the corneal epithelium (Fig 4). Our findings for laminin in the human cornea are in agreement with previously described immunohistochemical results for human cornea at the light microscopical level.[21]

Discussion

Laminin is a large multidomain glycoprotein which together with collagen type IV and heparan sulphate proteoglycan (HSPG) comprises most of the protein found in basement membranes.[22] The extracellular matrix possesses important regulatory properties governing cell behaviour.[23] More specifically, basement membranes are specialised sheets of extracellular matrix directly involved in a number of important biological processes, such as cell adhesion and orientation.[24] Moreover, it is thought that individual components within basement membranes are responsible for particular functions. Thus collagen type IV forms network structures which provide the structural scaffold on to which the other components are assembled,[25] whereas HSPG maintains the filtration properties of basement membranes.[22]

Laminin promotes the structural integrity of basement membranes through specific binding with collagen type IV and HSPG, but of greater importance is its functional contribution to basement membranes. It has been shown that laminin promotes cell adhesion, migration, and growth and has an active role in tissue restoration.[26 27] These functions are associated with specific functional domains within the laminin molecule. For example, the mitogenic and cell attachment activities are two distinct functions controlled by separate laminin domains.[28]

It is surprising that so little attention has been paid to the distribution of laminin in the normal iris considering that the iris has many unique structural and functional properties. This information is obviously necessary in order the better to comprehend the functional role of laminin in iris.

It was of interest to note the distribution of laminin in the normal iris vasculature. Labelling for laminin was restricted principally to the extracellular matrix enclosing the myocytes within the walls of the larger iris vessels. A similar pattern was also observed in smaller vessels when labelling was observed round contractile cells but not beneath the vascular endothelium (Fig 1A). The same localisation pattern for laminin was reported in a recent immunocytochemical study of cat retinal vessels.[29] This pattern of laminin distribution may indicate that within the iris vasculature the synthesis of laminin is a responsibility of the myocytes and pericytes rather than the endothelial cells. Our conclusion is based on the assumption that cells attached to basement membranes secrete most if not all the extracellular matrix components present within that basement membrane.

By contrast, in a previous study[15] we have shown that there was more intense labelling for collagen type IV in the subendothelial basement membrane of iris vessels in comparison with the matrix round vessel supporting cells. Consequently we consider that in iris vessels endothelial cells assemble primarily collagen type IV while laminin is mainly produced by myoepithelial cells and pericytes. This is important, as differences in the production and utilisation of laminin may contribute to variations in cell behaviour. It is relevant that a recent in-vitro study demonstrated that aortic endothelial cell adhesion is preferentially promoted by collagen type IV in comparison with laminin.[27]

It has recently been emphasised that the chemical composition of basement membranes may vary according to the demands of particular tissues.[22] The observation that in the normal iris laminin seems to be mainly present in the walls of thicker vessels indicates heterogeneity in the components of thick and thin basement membranes within the iris. Our findings are in accord with an immunogold quantitative study performed on a variety of animal basement membranes.[30]

With reference to the label exhibited for laminin in the matrix in which the dilator muscle is embedded, we suggest that in this instance laminin may be acting as an adhesive factor. Its presence in the matrix may be instrumental for the orderly contraction of the dilator muscle. Therefore changes in its distribution within this matrix could conceivably interfere with the dilatation of the iris.

The intense labelling associated with the filamentous bundles bordering iris stromal fibrocytes is more difficult to interpret, as the functional role of these cells remains unclear. However, a recent ultrastructural study has demonstrated a layer of iris fibrocytes separating the dilator muscle cells from the iris stroma, and it postulated that these fibrocytes played a role in the innervation of the dilator muscle.[31]

There is accumulating evidence that alterations in the interaction between cells and their matrices can precede and may eventually result in ocular tissue malfunction.[21,32,33]

It is conceivable that during the aging process quantitative alterations of specific extracellular matrix components occur within ocular tissues and may result in functional impairment. Such a process could account for the reduction of laminin associated with aging in our material. Nevertheless, the effect of aging on the quantity of laminin can be confirmed only with the use of an immunogold quantitation technique.

To the best of our knowledge this is the first investigation that has shown laminin to be an integral component of exfoliation material. An intense specific label associated with exfoliation aggregates was obtained in all seven specimens. Labelling was principally present on the exfoliation fibres, with a low density of label associated with the interfibrillar matrix. At high magnification immunolabelling was shown to be evenly distrubted over the exfoliation fibres. Moreover, the labelling density increased with increasing density of exfoliation deposits. Therefore our results demonstrate that laminin constitutes an integral component of the exfoliation fibres and to a less extent to that of the interfibrillar matrix.

We were intrigued to find that labelling was markedly reduced in the basement membrane of exfoliation-free iris vessels. Within the vessels containing exfoliation material the immunogold label was predominantly localised to the exfoliation material. However, it was not possible to be certain that laminin was depleted from basement membranes in exfoliation-positive iris vessels, since exfoliation material was intermingled with those basement membranes.

The reduction of laminin in exfoliation-free vascular basement membranes may reflect an abnormal pattern of laminin utilisation. This suggests that laminin, which normally is incorporated into basement membrane, is being diverted to the formation of exfoliation material. This is not surprising, as the cells that produce the matrix components for the ocular basement membranes are probably the same as those proposed for the synthesis of exfoliation material.[10,13,14] The triggering mechanism behind this functional conversion awaits clarification, though a metabolic mechanism has been suggested.[13,14]

The absorption of laminin from the iris vascular basement membranes and the ensuing alterations of its binding with the other basement membrane constitutents, like HSPG and collagen type IV, could compromise the structural integrity and the filtration properties of iris vascular basement membranes. This underlying mechanism may account for the increased permeability of exfoliative iris vessels visualised by fluorescein angiography.[34]

Another point of clinical interest was the relationship between exfoliation material and the iris dilator muscle. In four exfoliative specimens there was extensive infiltration of the dilator muscle extracellular matrix with laminin labelled exfoliative fibres (Fig 2B). This phenomenon, together with a potential alteration of the laminin distribution in the embedding matrix of the dilator muscle, could account for the impaired dilatation commonly seen in patients with exfoliation syndrome and glaucoma.[35]

The adhesive properties of laminin are well documented.[26,27] It may be instrumental in the adherence of exfoliation aggregates to ocular structures, such as the anterior hyaloid face and corneal endothelium.

The relationship between exfoliation material and ocular basement membranes has been the subject of fierce speculation over the last few decades. Ultrastructural studies have already documented a number of morphological features that support this relationship.[36-40] These features in the iris comprise (*a*) the proximity of exfoliation material to basement membranes, and (*b*) the marked ultrastructural changes caused by exfoliation deposition on the iris vascular basement membranes. At a late stage these membranes may be almost entirely replaced by exfoliation material.[39-41] This association became more apparent after a three-dimensional reconstruction study[40] of exfoliation deposits and iris vessels; many stromal deposits were traced back to the vessel wall.

Despite the fact that most investigators in the field have favoured the involvement of basement membrane producing cells in the production of exfoliation material,[10,13,14,40] there is less agreement on whether or not exfoliation material contains basement membrane components. Evidence has already been advanced to indicate that exfoliation material contains glycoproteins[3,7] and proteoglycans,[4,6] which are major components of basement membranes. However, a number of investigations have repeatedly shown an association between exfoliation material and components of the elastic system, namely, oxytalan[8,9] and elastic-like materials.[10-12] These components, with the possible exception of amyloid P,[22] are not thought to be normal basement membrane constituents. Nevertheless, on the grounds of the variations seen in the histochemical staining properties it is clear that exfoliation material is a composite of more than one substance.[5,9] Thus it is likely that elastin and other constituents are produced as part of an aberrant extracellular matrix synthesis. This process is probably orchestrated by basement membrane producing cells. Our results suggest that, within the iris vasculature, exfoliation material is synthesised by contractile cells.

In conclusion, we hypothesise that the synthesis of exfoliation material is initiated at the molecular level by an aberrant basement membrane biosynthesis, which results in laminin being incorporated into the exfoliation material. The main challenge, however, remains the identification of this aberration as a first step towards prevention of this common blinding disorder.

We thank Shahida Abraham for expert technical assistance and Pat Bonnar for secretarial assistance. We are also grateful to Drs J L Jay, J Dudgeon, G N Dutton, R L Burton, and H Hammer for the supply of specimens and facilitating our access to their patients

This study was supported by a grant from the W H Ross Foundation ([Scotland).

1 Forsius H. Exfoliation syndrome in various ethnic populations. *Acta Ophthalmol (Kbh)* 1988; 66 (suppl). 71–85.

2 Jerndal T. Open angle glaucoma and the pseudo-exfoliation syndrome. In: Cairns JE, eds. *Glaucoma* London: Grune and Stratton, 1986: 661–77.

3 Morrison JC, Green WR. Light microscopy of the exfoliation syndrome. *Acta Ophthalmol (Kbh)* 1988; 66: (suppl): 5–27.

4 Davanger M Pseudo-exfoliation material. Electron microscopy after the application of lanthanum as tracer particles and ionic stain. *Acta Ophthalmol (Kbh)* 1980: 58: 512–9.

5 Ringvold A. Exfoliation syndrome. Immunological aspects. *Acta Ophthalmol (Kbh)* 1988; 66 (suppl): 35–43.

6 Harnisch JP, Barrach HJ, Hassel JR, Sinha PK. Identification of a basement membrane proteoglycan in exfoliation material. *Graefes Arch Clin Exp Ophthalmol* 1981; 215: 273–8.

7 Streeten BW, Gibson SA, Li ZY. Lectin binding to pseudoexfoliative material and the ocular zonules *Invest Ophthalmol Vis Sci* 1986; 27: 1516–21.

8 Garner A, Alexander RA. Pseudoexfoliative disease: histochemical evidence of an affinity with zonular fibres. *Br J Ophthalmol* 1984; 68: 574–80.

9 Streeten BW, Dark AJ, Barnes CW Pseudoexfoliative material and oxytalan fibres. *Exp Eye Res* 1984; 38: 523–31.

10 Streeten BW, Gibson SA, Dark AJ. Pseudoexfoliative material contains an elastic microfibrillar-associated glycoprotein *Trans Am Ophthalmol Soc* 1986; 84: 304–20

11 Li ZY, Streeten BW, Wallace RN. Association of elastin with pseudoexfoliative material. an immunoelectron microscopic study Curr Eye Res 1988; 7: 1163–72.

12 Li ZY, Streeten BW, Yohai N. Amyloid P protein in pseudoexfoliative fibrillopathy *Curr Eye Res* 1989; 8: 217–27.

13 Eagle RC, Font RL, Fine BS. The basement membrane exfoliation syndrome. *Arch Ophthalmol* 1979; 97: 510–5.

14 Dark AJ, Streeten BW. Pseudoexfoliation syndrome. In: Garner A, Klintworth G, eds. *Pathobiology of ocular disease A dynamic approach*. New York· Dekker, 1982. 1303–20

15 Marshall GE, Konstas AG, Lee WR. Immunogold localization of type IV collagen and laminin in the aging human aqueous outflow system. *Exp Eye Res* in press.

16 Marshall GE, Konstas AG, Lee WR. Ultrastructural distribution of collagen types I-VI in aging human retinal vessels *Br J Ophthalmol* 1990; 74: 228–32.

17 Prince AM, Streeten BW, Ritch R, Dark AJ, Sperling M. Preclinical diagnosis of pseudoexfoliation syndrome. *Arch Ophthalmol* 1987; 105: 1076–82.

18 Shakib M, Ashton N, Blach R. Electron microscopic study of pseudoexfoliation of the lens capsule. II. Iris and ciliary body. *Invest Ophthalmol Vis Sci* 1965, 4: 154–61.

19 Jay JL, Murray SB. Early trabeculectomy versus conventional management in primary open angle glaucoma. *Br J Ophthalmol* 1988, 72: 881–9.

20 Konstas AG, Marshall GE, Lee WR. Immunocytochemical localization of collagens (I-V) in the human iris. *Graefes Arch Clin Exp Ophthalmol* 1990; 228: 180–6

21 Ben-Zvi A, Rodrigues MM, Krachmer JH, Fujikawa LS. Immunohistochemical characterization of extracellular matrix in the developing human cornea *Curr Eye Res* 1986; 5: 105–17.

22 Abrahamson DR. Recent studies on the structure and pathology of basement membranes. *J Pathol* 1986; 149: 257–78

23 Abbot NJ. The milieu is the message. *Nature* 1988; 332: 490–1

24 Martin GR, Timpl R. Laminin and other basement membrane components. *Ann Rev Cell Biol* 1987; 3: 57–85

25 Schnittny JC, Timpl R, Engel J. High resolution immunoelectron microscopic localization of functional domains of laminin, nidogen and heparan sulphate proteoglycan in epithelial basement membrane of mouse cornea reveals different topological orientations *J Cell Biol* 1988, 107: 1599–610

26 Engel J. EGF-like domains in extracellular matrix proteins: localized signals for growth and differentiation? *FEBS Lett* 1989; 251: 1–7.

27 Herbst TJ, McCarthy JB, Tsilibary EC, Furcht LT Differential effects of laminin, intact type IV collagen and specific domains of type IV collagen on endothelial cell adhesion and migration *J Cell Biol* 1988; 106: 1365–73.

28 Panayotou G, End P, Aumailley M, Timpl R, Engel J Domains of laminin with growth factor activity *Cell* 1989, 56: 93–101

29 Essner E, Lin WL. Immunocytochemical localization of laminin, type IV collagen and fibronectin in cat retinal vessels. *Exp Eye Res* 1988; 47: 317–27.

30 Grant DS, Leblond CP. Immunogold quantitation of laminin, type IV collagen and heparan sulphate proteoglycan in a variety of basement membranes. *J Histochem Cytochem* 1988; 36: 271–83.

31 Sugita A, Ishibashi R, Shiotani N, Yoshioka H Morphological features of iris fibroblasts in dilator muscle region *Jpn J Ophthalmol* 1988; 32: 151–8.

32 Glaser BM. Extracellular modulating factors and the control of intraocular neovascularization. *Arch Ophthalmol* 1988; 106: 603–6 .

33 Caldwell RB Extracellular matrix alterations precede vascularization of the retinal pigment epithelium in dystophic rats. *Curr Eye Res* 1989, 8: 907–21.

34 Vannas A. Fluorescein angiography of the vessels of the iris in pseudoexfoliation of the lens capsule, capsular glaucoma and some other forms of glaucoma. *Acta Ophthalmol (Kbh)* 1969; 105 (suppl). 9–75

35 Carpel EF. Pupillary dilatation in eyes with pseudoexfoliation syndrome. *Am J Ophthalmol* 1988, 105: 692–94.

36 Ringvold A Light and electron microscopy of the wall of iris vessels in eyes with and without exfoliation syndrome *Virchows Arch (A)* 1970; 349: 1–9

37 Ringvold A. The distribution of exfoliation material in the iris from eyes with exfoliation syndrome. *Virchows Arch (A)* 1970, 351: 168–78.

38 Anastasi G, Puzzolo D, Romeo G, Santoro A, Scullica L Iris ultrastructural changes in senile pseudoexfoliation *Ophthalmologica* 1974; 168: 109–21

39 Ghosh M, Speakman JS. The iris in senile exfoliation of the lens. *Can J Ophthalmol* 1974, 9: 289–97.

40 Shimizu T. Changes of iris vessels in capsular glaucoma three dimensional and electron microscopic studies *Jpn J Ophthalmol* 1985, 29: 434–52.

41 Dickson DH, Ramsey MS. Fibrillopathia epitheliocapsularis. Review of the nature and origin of pseudoexfoliative deposits *Trans Ophthalmol Soc UK* 1979; 99: 284–92,

British Journal of Ophthalmology, 1990, 74, 458–461

Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules

A P Watson, E S Rosen

Southport District General Hospital, Southport
A P Watson

Manchester Royal Eye Hospital, Oxford Road, Manchester
E S Rosen

Correspondence to
A P Watson, FRCS, District General Hospital, Southport, Merseyside PR8 6NJ

Accepted for publication
15 February 1990

Abstract

Injection of fluorescein intravenously for fundal angiography is associated with a high incidence of minor adverse effects (21%) but a very low incidence of serious (life threatening) reactions (0·05%). A serious reaction may occur without warning in a patient with no history of atopy. There are no reports of oral fluorescein causing a serious reaction, and minor adverse effects are uncommon. A study was undertaken to determine optimum conditions for oral fluorescein angiography. Capsules proved more convenient than a solution for ingestion of fluorescein. A dose of 25 mg/kg body weight produced good quality angiograms in 75% of the patients. The best pictures were obtained by photographing the fundus after 40 and 60 minutes.

Fluorescein fundal angiography (FFA) has become progressively established as a valuable clinical investigation since the technique was described in detail in 1961.[1] When fluorescein is given intravenously reactions can occur. Giving the fluorescein orally makes the risk of a serious reaction minimal and greatly reduces the incidence of minor reactions. Previous authors have already reported that good quality angiograms can be produced with oral fluorescein,[2-6] though high intensity early passes do not occur.

The aims of this study were to evaluate the use of oral fluorescein in capsule form, to determine if there is a dose which will reliably give good quality angiograms, and to discover the best time to photograph the fundus after the capsules have been taken.

Materials and methods

After the approval of the ethical committee 20 healthy volunteers were recruited from the staff of Manchester Royal Eye Hospital and were asked to give written consent. The subjects were asked to fast for six hours before being given a test dose of 10 mg of fluorescein in liquid form and being weighed. If over the next half hour they experienced no symptoms such as faintness, warmth, or itching suggestive of an allergic reaction, they were then given a larger dose in capsule form.* The patients were randomly assigned to one of five groups, to be given 1, 1·5, 2, or 2·5 g of fluorescein. One pupil was dilated with tropicamide 1%, plus phenylephrine 10% if necessary.

Fundal photographs were taken with either a Canon CF-60U or Kowa Pro I fundus camera 20, 30, 40 and 60 minutes after the capsules had been swallowed. The film used was Ilford FP4 rated to 800 ASA. The films were developed in Kodak D76 for 30 minutes at 20°C.

Results

The 80 angiograms were graded into four categories: 3=strong fluorescence; 2=moderate fluorescence; 1=faint fluorescence; 0=no useful fluorescence.

Grade 3 angiograms were comparable in quality with those produced by intravenous fluorescein. Grade 2 angiograms were also of good quality, and any abnormal leakage would be readily seen. In the grade 1 angiograms the disc and macula could be distinguished and it would be possible to recognise any major leakage. However, small amounts of late leakage might be missed. Grade 0 angiograms did not show any significant degree of fluorescence, and fundal features could not be distinguished. Examples of angiograms from categories 1, 2, and 3 are shown in Figure 1.

For 15 of the 20 volunteers one or more angiograms in grade 2 or 3 were produced, and 12 of these 15 had one or more grade 3 angiograms. All except one had been given a dose of fluorescein equivalent to at least 25 mg/kg body weight. The best quality angiograms were obtained at 40 or 60 minutes after they had taken the capsules, though good quality angiograms could also be obtained at 30 minutes in some cases. An example of progression of fluorescence in successive angiograms is shown in Figure 2.

For five of the 20 subjects no useful angiograms were obtained. In four of these five there was no visible fluorescence. Although two of the five had been given fluorescein equivalent to less than 15 mg/kg body weight, the other three had received a dose of over 30 mg/kg.

None of the subjects experienced any reaction to the test dose of liquid fluorescein. After taking the capsules one person developed a mild urticarial rash on the extensor surfaces of her arms and legs. She experienced no other ill effects. She was given chlorpheniramine maleate 4 mg by mouth, and the rash resolved over the next four hours.

Discussion

Fluorescein was first synthesised in 1871. It was

---

*Capsules of sodium fluorescein 500 mg were formulated and prepared by Jill Bumphrey, MPS, at the Leicestershire Health Authority District Pharmacy, Leicester Royal Infirmary, Leicester. The raw material specification was fluorescein sodium BP, NWRHA specification, supplied by Société Chimique Pointet Gorard The pharmacy can supply the capsules at a cost of approximately £10 per 100

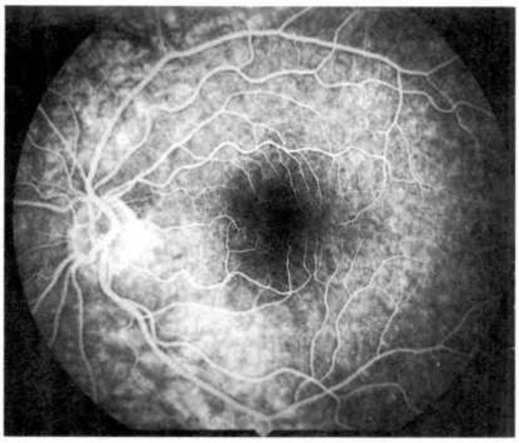


Figure 1A: Grade 3

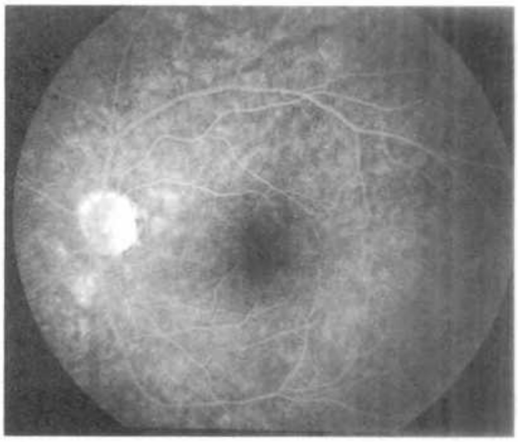


Figure 1B: Grade 2.

Figure 1: Examples of different grades of angiogram.

used in the examination of the fundus in Germany in 1910[7] and in a study of a patient in the USA with abnormal aqueous dynamics in the Sturge-Weber syndrome in 1932.[8] By 1943 its use was recommended as an adjunct to ocular examination in Duke-Elder's *Textbook of ophthalmology* published in the UK and USA.[9]

In modern ophthalmic practice fluorescein fundal angiography (FFA) can provide valuable information about the retinal circulation, the integrity of the blood-retinal barrier, and the health of the retinal pigment epithelium.[10] Intravenous fluorescein angiograms are of a reliably high quality if the ocular media are clear. The fluorescein is usually given intravenously, and, as with almost any agent given by this route, there is a risk of provoking a reaction. Most reactions to intravenous (IV) fluorescein are mild, but a small proportion are serious and occasionally fatal.

Mild reactions include nausea, vomiting, chills or warmth, hypersalivation, dizziness, urticaria, itching, and facial oedema. The following serious reactions have been reported: wheezing, laryngeal oedema, bronchospasm, pulmonary oedema, respiratory arrest, basilar artery ischaemia, atrial fibrillation, chest pain, myocardial infarction, loss of consciousness, and shock.[11-16] Skin necrosis may occur if there is extravasation of the fluorescein.[17]

The incidence of reactions is not easy to establish from the literature. In a prospective study where reactions to IV fluorescein were ascertained by asking each patient to describe any unpleasant sensations, as well as by observation, an incidence of 21% was reported,[18] though all these were mild. In a retrospective study reviewing the records of a number of different institutions in the USA another study found the incidence of reactions to be 0·6%, but of these the majority (66·6%) were severe.[11] Figures from other studies lie between the two extremes, suggesting that mild reactions are common, occurring in about 20% of injected patients, but that life threatening reactions are rare, occurring in less than 0·05% of patients. This risk factor is nevertheless significant for a procedure which is most commonly undertaken in situations where life is not threatened by the condition being investigated.

There is greater likelihood of a reaction to IV fluorescein in a patient with a history of atopy or drug reactions,[11] but a life threatening reaction, such as acute pulmonary oedema, may occur in a patient who is not atopic and has no respiratory disease.[12]

The precise nature of reactions to IV fluorescein is not clear. Some may be due to hypersensitivity (anaphylaxis) as a result of an immunological response of the host to a hapten (drug)-protein combination. Yet the proportion occurring in patients who have received previous injections is not much greater than in patients exposed to fluorescein (in large amounts) for the first time. It is hard to imagine how people who have not been previously injected could become sensitised to fluorescein either through topical applications to their eyes or from the environment. Skin testing with both fluorescein and fluorescein-conjugated human serum albumin (F-HSA) in three patients who had suffered reactions to IV fluorescein yielded only one positive result, and that was to F-HSA.[11]

Raised serum histamine levels have been found after the administration of IV fluorescein to people who have experienced a reaction, but also in a large proportion of those who experienced no ill effects.[18] In spite of the finding of raised levels in unaffected patients, these results do suggest that histamine plays a part in the production of reactions to IV fluorescein. Apart from its role in anaphylaxis, histamine may also be released (in vitro) in the absence of an antigen-antibody reaction.[19]

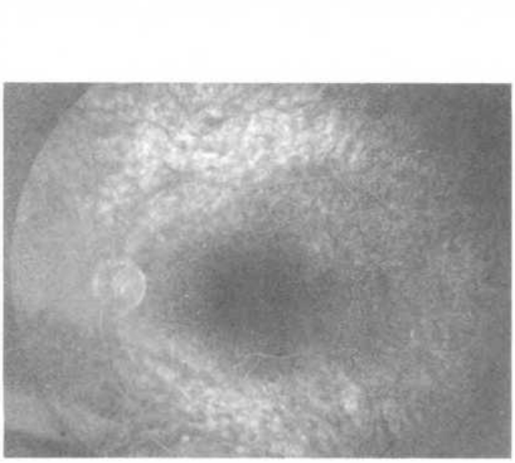


Figure 1C: Grade 1.

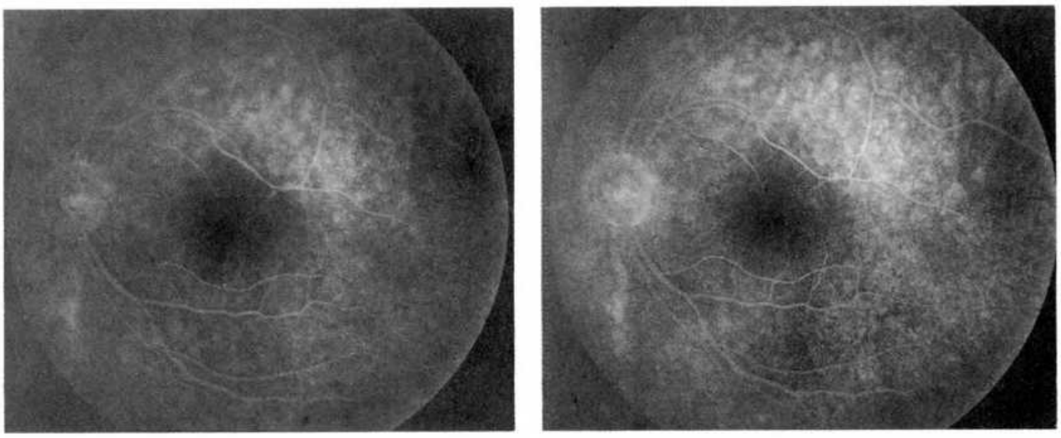


Figure 2A: 20 minutes.

Figure 2B: 30 minutes.

Figure 2: Successive angiograms in an individual.

It may also have been of importance that in the past the solutions of fluorescein used for FFA contained significant quantities of contaminants. Metallic and ionic mercury were found in samples in the USA in 1970,[11] and after a number of serious reactions in the UK high levels (up to 2%) of dimethyl formamide were isolated.[20] At that time dimethylformamide was difficult to eliminate entirely during the manufacture of fluorescein, and an upper limit specification of 0·2% was set by the Department of Health and Social Security.[21]

A serious reaction to any potentially allergenic agent is much less likely if it is administered orally rather than systemically. As described in the introduction, fluorescein has been administered orally for many years and has recently been used by an increasing number of investigators. To the best of our knowledge no serious reaction to oral fluorescein has ever been reported. There is only one previously reported 'mild allergic reaction',[3] and one of our volunteers developed a mild, transient, urticarial rash.

Oral fluorescein produces good quality angiograms in most cases provided it is not necessary to have early phase, high intensity pictures. Angiograms from oral fluorescein have already been shown to be useful in the demonstration of cystoid macular oedema,[2 3 6 22] papilloedema,[19 23 24] and central serous retinopathy.[5] The advantages of oral fluorescein are that it need not be given by a doctor, patients with inaccessible veins can be investigated, children or adults who are afraid of injections are not alarmed, and it is safer than intravenous fluorescein.

As fluorescein capsules have not previously been available, it has been customary to give oral fluorescein in liquid form, from phials manufactured for intravenous use. The disadvantages of liquid fluorescein are that it looks and tastes unpleasant (even when mixed with fruit juice or cordial), that it temporarily stains teeth, and that, if there is any spillage on to clothes, the results are spectacular. The use of capsules avoids all these problems.

Our results indicate that a dose of 25 mg/kg body weight produces good quality angiograms in 75% of patients. In order to provide comparable results the volunteers for this study were asked to fast before taking the fluorescein, but from earlier experience the authors have found that this is not essential, and for patients with diabetes mellitus it is inadvisable to recommend fasting before oral fluorescein angiography.

In this study the best pictures were obtained by photographing the fundus at 40 and 60 minutes after the capsules had been taken. We recommend the use of oral fluorescein in capsule form when early, high intensity, angiograms are not required, on the grounds of efficiency, convenience, and safety.

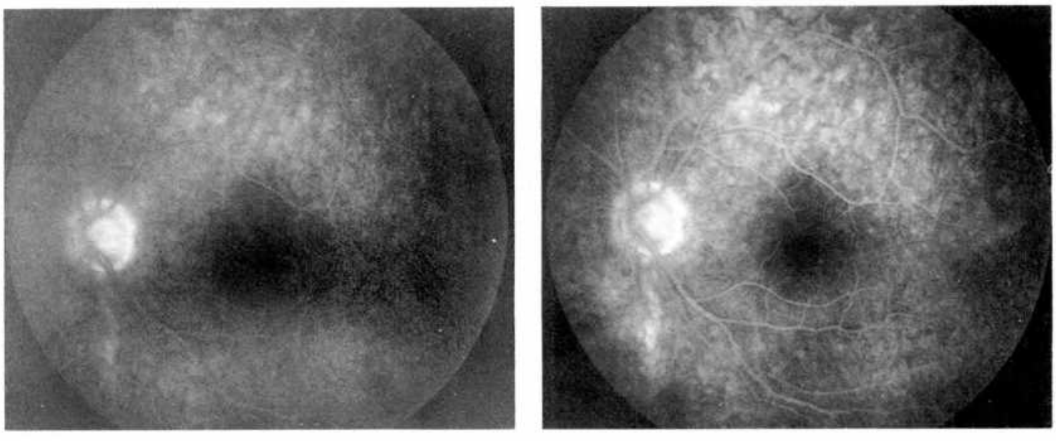


Figure 2C: 40 minutes.

Figure 2D: 60 minutes.

All the photographs were taken by Richard Hancock (general medical photographer) and Adam Prest (medical research photographer), whose skill and commitment enabled this study to come to a successful conclusion.

The authors wish to thank those friends and colleagues at Manchester Royal Eye Hospital who volunteered to take oral fluorescein for this study, which would not have been possible without their involvement

1 Novotny HR, Alvis DL A method of photographing fluorescence in circulating blood in the human retina *Circulation* 1961; 24: 82–6.

2 Kelley JS, Kincaid M. Retinal fluorography using oral fluorescein *Arch Ophthalmol* 1979, 97: 2331–2.

3 Kelley JS, Kincaid M, Hoover RE, McBeth C. Retinal fluorograms using oral fluorescein *Ophthalmology* 1980; 87: 805–11

4 Oral fluorescein study group. Oral fluorography. *J Am Optom Assoc* 1985; 56: 784–92.

5 Azad R, Nayak BK, Tewari HK, Khosola PK Oral fluorescein angiography *Indian J Ophthalmol* 1984, 32: 415–7.

6 Noble MJ, Cheng H, Jacobs PJ. Oral fluorescein and cystoid macular oedema detection in aphakic and pseudophakic eyes *Br J Ophthalmol* 1984; 68: 221–4.

7 Burk A. Die klinische, physiologische und pathologische Bedeutung der Fluoreazenz in augenach Darreichung von Uranin. *Klin Monatsbl Augenheilkd* 1910; 48: 445–54.

8 Tyson HH Nevus flammeus of the face and globe associated with glaucoma, vascular changes in the iris and a calcified vascular growth in the occipital lobe of the brain, with right homonymous hemianopia. *Arch Ophthalmol* 1932; 8: 365–71

9 Duke-Elder S *Textbook of ophthalmology* London: Kimpton, 1943: 2: 1150.

10 Rosen ES *Fluorescence photography of the eye.* London Butterworths, 1969

11 Stein MR, Parker CW Reactions following intravenous fluorescein *Am J Ophthalmol* 1971; 72: 861–8

12 Hess JB. Pacurariu RJ. Acute pulmonary edema following intravenous fluorescein angiography. *Am J Ophthalmol* 1976, 82: 567–70.

13 Kirson LE, Wilson ME Atrial fibrillation associated with intravenous fluorescein *Anesth Analg* 1987, 66: 283

14 Butner RW, McPherson AR Adverse reactions in intravenous fluorescein angiography *Ann Ophthalmol* 1983, 15: 1084–6

15 Karhunen U, Raitta C, Kala R Adverse reactions to fluorescein angiography *Acta Ophthalmol (Kbh)* 1986, 64: 282–6.

16 Yannuzzi LA, Roherer KT, Tindel LG, *et al* Fluorescein angiography complication survey *Ophthalmology* 1986, 93: 611–7.

17 Elman MJ, Fine SL, Sorenson J, *et al* Skin necrosis following fluorescein extravasation A survey of the macula society *Retina* 1987, 7: 89–93

18 Arroyave CM, Wolbers R, Ellis PP Plasma complement and histamine changes after intravenous administration of sodium fluorescein. *Am J Ophthalmol* 1979; 87: 474–9.

19 Eustace P, Travers S, Mooney D Oral Fluorescein angiography in disc oedema *Bull Soc Belge Ophtalmol* 1984; 211: 35–41

20 Jacob JSH, Rosen ES, Young E Report on the presence of a toxic substance, dimethyl formamide, in sodium fluorescein used for fluorescein angiography *Br J Ophthalmol* 1982, 66: 567–8

21 Buckley H. Fluorescein injection DHSS communication Reference no. 2–10/81 23 June 1982

22 Morgan KS, Franklin RM. Oral fluorescein angioscopy in aphakic children *J Pediatr Ophthalmol Strabismus* 1984, 21: 33–6.

23 Ghose S, Nayak BK Role of oral fluorescein in the diagnosis of early papilloedema in children *Br J Ophthalmol* 1987, 71: 910–5

24 Bynke HG Differentiation of papilloedema from pseudopapilloedema by fluorescein ophthalmoscopy *Acta Ophthalmol (Kbh)* 1970, 48: 752–8.

British Journal of Ophthalmology, 1990, 74, 462–464

Artificial maintenance of the relative ocular tissue pressure during eye surgery

C Maggi, R Maggi

8 Via Latina, 00179 Rome, Italy
C Maggi
R Maggi

Correspondence to:
C Maggi, MD.

Accepted for publication
15 February 1990

Abstract

We describe an operating table in which the whole patient, apart from the eye undergoing surgery, is enclosed in a caisson within which the barometric pressure can be lowered at any time during surgery. This increases the effect of atmospheric pressure on the eye, enabling 'open sky' surgery to be carried out on patients of any age.

In mammals the rigidly enclosed organs such as the eyeball or the brain have their tissue pressure maintained by the fixed volume of the enclosed liquids which are in constant balance with the pressure of the vascular network. This balance is controlled by a blood-brain or blood-aqueous barrier,[1] in accordance with the law of Monro-Kellie.[2] Any sudden change in volume of the liquids, such as during surgery, disrupts this balance of pressure across the vascular walls and subverts the dynamics of the local blood circulation.[3]

The eyeball is enclosed in the bony cavity of the orbit, open only to the exterior. By separating the operating field, including the eye, by a rigid adhesive membrane from the rest of the body which is enclosed in a caisson (similar to a hyperbaric chamber) a difference in pressure can be regulated on both sides of the separation, either by increasing the atmospheric pressure in the room,[4] or by decreasing the atmospheric pressure on the patient's respiratory system. We describe a new device for raising the relative atmospheric pressure on the contents of the eye during surgery.

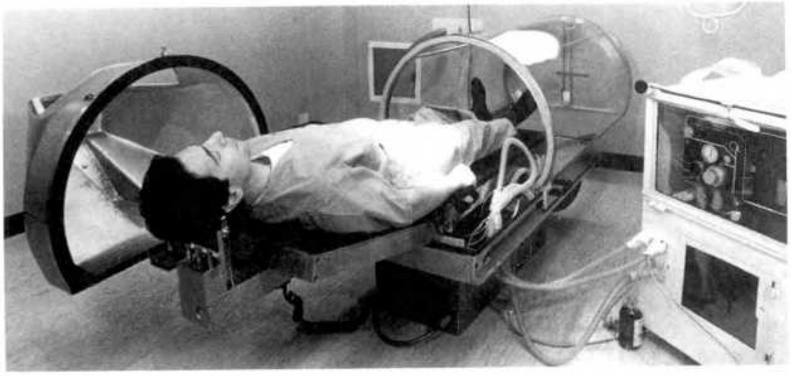


Figure 1A

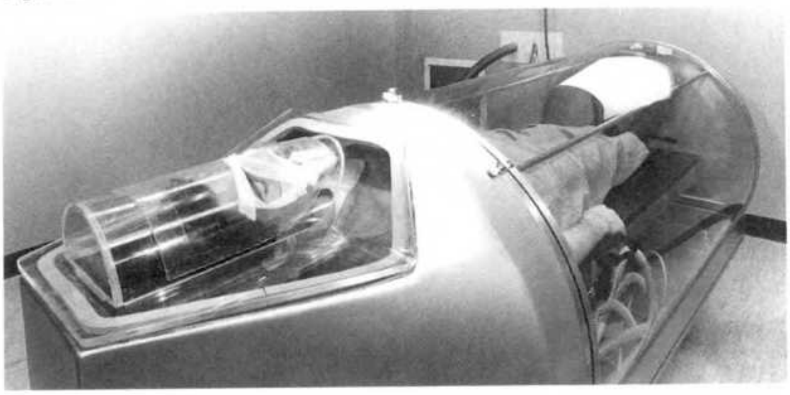


Figure 1B

Figure 1: The operating table before (A) and after (B) airtight closure. Note the sealed container for the pulmonary ventilator, which is in communication with the caisson to maintain the same ambient pressure.

Materials and methods

The patient is enclosed in an airproof container (caisson), and the orbital rim is sealed to a hole suitably situated in it (Fig 1A, 1B). With a vacuum pump the environmental pressure inside the airtight container is decreased by 15 mmHg – that is the average intraocular pressure. On the eye being opened the loss of aqueous causes a fall of the intraocular pressure to the level of that existing on the exterior of the caisson.

In these conditions the loss of the liquid volume of the eye removes any influence on the haemodynamics of the eye, which is now directly influenced by the relative compression resulting from the difference in pressure on the inside and outside of the caisson, and monitored by the suction pump. A normal turnover of the aqueous in the leaking eye allows safe open-sky surgery for any length of time desired.

If the vena cava pressure is monitored in the proximity of the right atrium when the pressure inside the caisson is decreased, a parallel change in the central venous pressure from positive to negative is found to take place. There is invariably a clearly visible sinking of the eye in the orbit, which is now depleted of venous blood.

In the surgically opened eye the loss of tissue pressure against the thin walls of the choroidal veins is now balanced by the negative pressure already established in the vena cava, and no increase in the venous volume of the choroid occurs. In the same way, on the arterial side, the normal difference in pressure between the left ventricle and the intraocular capillaries is equally maintained, as the lowering of the peripheral resistance following the opening of the eye is balanced by a parallel decrease in the absolute pressure of the left ventricle. The blood pressure, if measured inside the depressurised caisson, remains unchanged, being merely relative to the patient's atmospheric pressure. Thus a normal gradient of pressure is re-established on both the arterial and the venous side of the intraocular capillary network in spite of the sclera being open. Normal anaesthetic monitoring and safety can be maintained by the caisson.

A safety valve in the caisson is regulated at a pressure of 40 cm of water, preventing an inadvertent excessive decrease in the ambient pressure on the patient's body. In any emergency the pump is stopped and the interior pressure returns to normal within three seconds. This allows manual opening of the cover and free access to the patient's body but leaves the sterile surgical field undisturbed. In general anaesthesia a pulmonary ventilator is used. This is enclosed in an airproof container at the same pressure as that acting on the patient's body (Fig 1A).

In conventional eye surgery when the sclera is opened several undesirable consequences occur: in the valveless intraocular veins the blood outflow (which relies on the tissue pressure[5]) comes to a standstill, and venous engorgement follows. The thin walled veins, distended by the blood pooling, start leaking plasmoid fluid, upsetting the blood-aqueous barrier and causing stagnation in the subchoroidal space.[6,7] The resulting increase in the volume of the choroid progressively reduces the space available for the vitreous body, which in a long operation may bulge forward. In elderly patients the early loss of aqueous from the mostly liquefied vitreous gel makes more room for the swollen choroid,[8,10] and positive vitreous pressure becomes less noticeable in brief open-sky surgery. In babies and young patients, who have high scleral elasticity and a dense vitreous, scleral retraction and consequent vitreous prolapse soon follow. In these patients the wide limbal opening used in adults is considerably less safe.

The development of these events is prevented by the peroperative use of our technique, and open-sky surgery of any length can be safely performed in all patients, of any age or eye condition.

Results

Although this special operating table has been routinely used in all kinds of intraocular surgery, intracapsular cataract extraction in children is reported on in Table I as an example of open-sky surgery made possible with this technique. In none of these cases did intraoperative vitreous pressure occur. A small loss of vitreous occurred in six of the first cases as a result of an error in technique (undue pressure on the eyeball from the exterior) but did not cause late complications. Postoperative glaucoma occurred in two eyes after operation for traumatic cataract and needed surgery. A disinsertion of the retina occurred in one case of unilateral cataract three years after surgery.

In all cases the operation was carried out without any specific manoeuvres to prevent vitreous pressure such as the use of an eye compressor, hyperosmotic or hypotensive agents, or a scleral ring.

TABLE I *Intracapsular extraction*

	Year				
Age	*1–6 months*	*7–11 months*	*1–3 years*	*4–12 years*	*Total*
1979	–	1	1	–	2
1980	–	–	1	2	3
1981	3	2	1	2	8
1982	1	4	4	5	14
1983	1	10	5	6	22
1984	–	–	3	6	9
1985	2	3	2	5	12
1986	2	2	4	3	11
1987	7	1	4	7	19
1988	2	5	2	1	10
Total	18	28	27	37	110

The earliest intracapsular extraction took place at the age of 1 month In 42% of the 110 cases the operation was performed during the first year of life.

Discussion

This method, in 10 years' experience, has offered the following advantages.

Control of the vitreous pressure. The compression of the ocular contents greatly accelerates vitreous dehydration, already started by the opening of the scleral coat.[9] The dehydrated vitreous body is uniformly pressed against the scleral wall, compressing the choroid and preventing swelling. Vitreous loss becomes practically impossible even in the absence of the posterior capsule. If, after accidental external pressure, the vitreous undergoes prolapse, it can easily be repositioned with a spatula, because of the inverted vitreous pressure.

Peroperative hypotony. Once the pump is functioning, hypotony is immediately noted. Hyperbarism of 20 cm of water, the equivalent of intraocular pressure, is sufficient to achieve this result. Greater hypotony is available by further lowering the patient's environmental pressure in the caisson. No damage is possible from hypoxia, because the maximum relative orbital hyperbarism allowed by the pump is lower than the systolic pressure of the retinal arteries. If surgery is started at normal atmospheric pressure, and vitreous is under pressure, an immediate relative hypotony can be obtained merely by switching on the pump.

Intraocular space during surgery. A continuous flow of aqueous, in part normally produced and in part squeezed from the vitreous, maintains some depth of the anterior chamber, at least sufficient to prevent contact with the cornea during intraocular lens implantation. The anterior chamber can easily be kept full of air.

Because of the *preserved blood-aqueous barrier* during surgery very little aqueous flare can be noted postoperatively, and the routine use of mydriatics has proved unnecessary. Deposits on the implant have not been observed after surgery under hyperbarism.

The likelihood of retinal detachment, a frequent occurence in aphakic children,[11] is probably reduced by the lack of intraoperative forward displacement of the vitreous body due to the hyperbarism.

CONCLUSION

We propose that relative pneumatic hyperbaric compression of the eye during surgery, by means of the caisson operating table, maintains a normal intraocular pressure on the vascular network independently of the liquid volume of the eye, preventing choroidal swelling. Aqueous turnover and the blood-aqueous barrier are undisturbed during surgery. With the use of this technique an alternative to closed surgery is proposed with the aim of avoiding any disturbance to the anatomy of the eye.

In adult patients the avoidance of precautional hypotensive treatment and the immediate and harmless effect of hyperbarism on the eye soon come to be preferred by both the surgeon and the anaesthetist, once they become acquainted with the slight differences imposed by the new technique. In implant surgery the assurance of the intraocular spaces being maintained increases the confidence of the surgeon.

1 Kuriowa T, Cahn R, Huhler M, *et al.* Role of extra-cellular proteins in the dynamics of vasogenic brain edema *Acta Neuropathol (Berl)* 1978; 66: 3–11.
2 Brotch J. Les oedèmes cérébraux neurochirurgicaux, méchanisme d'incidence thérapeutique. *Rev Med Brux* 1986; 7: 217–9
3 Maggi C. L'iperbarismo settoriale in chirurgia oculistica *Boll Oculist* 1985; 65: 335–41.
4 Maggi C. Eye surgery in a new hyperbaric room. *Ophthalmol Proc* 1978, series 21: 347–57
5 Brubacker RF Editorial *Arch Ophthalmol* 1984; 102: 1753–4.
6 Jaffe N. *Cataract surgery and its complications.* St Louis Mosby, 1981. 127
7 Schepens CL Clinical and research aspects of subtotal open-sky vitrectomy. *Am J Ophthalmol* 1981; 91: 143–9
8 Robbins R, Galin MA. Effects of osmotic agents on the vitreous body *Arch Ophthalmol* 1969; 82: 694–9.
9 Robbins RM, Obstbaum SA, Galin MA. Intraocular pressure rebound *Br J Ophthalmol* 1971; 55: 177–82
10 Brubaker RF, Riley FC Vitreous body reduction in the rabbit. *Arch Ophthalmol* 1972; 87: 438–42.
11 Roussos J, Polychroniadis F. La décollement de la rétine suite à l'extraction de la cataracte *Ann Oculist (Paris)* 1973, 206: 315–9

FRIEDMANN 2

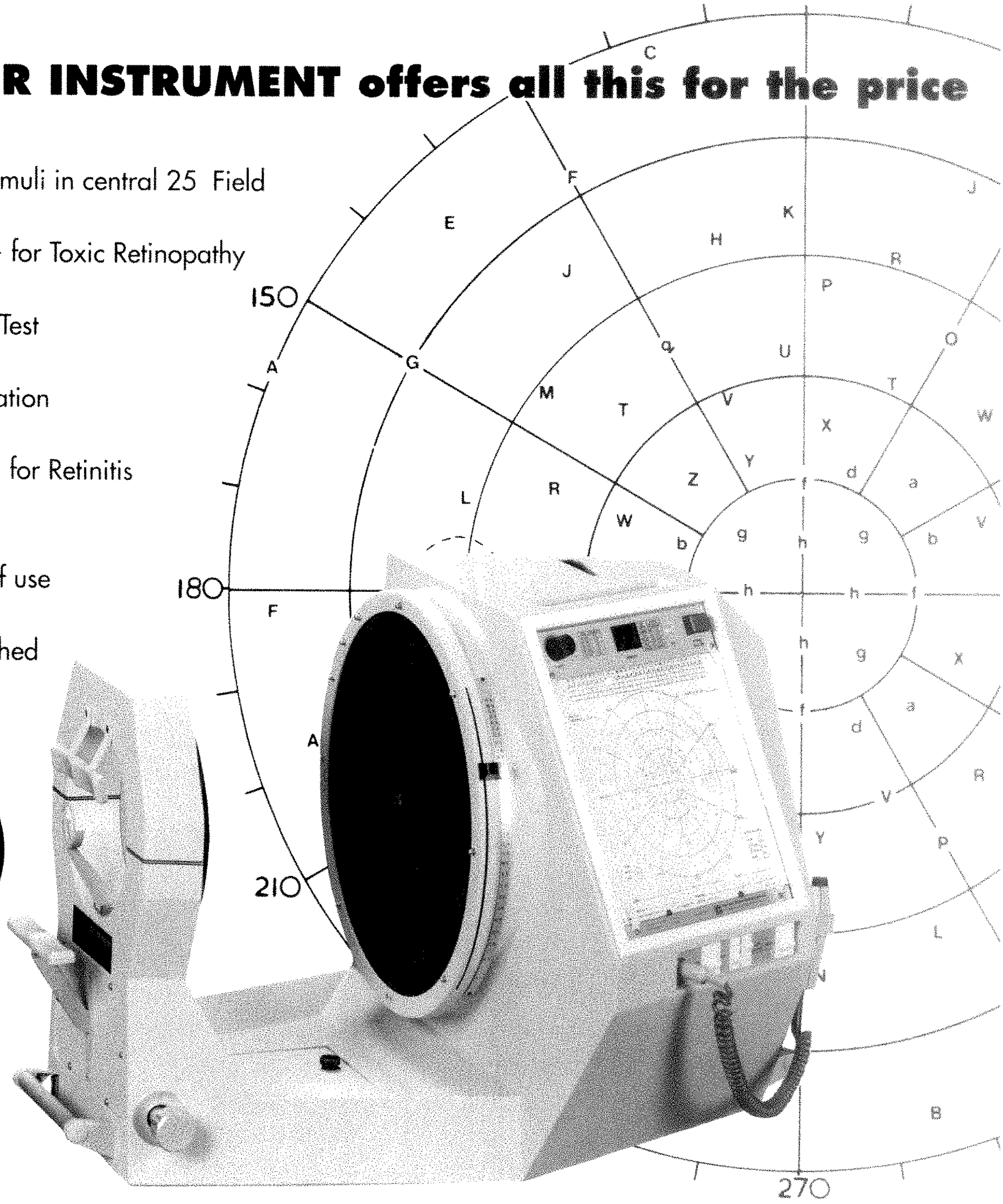
VISUAL FIELD ANALYSER

"Earlier at threshold"

NO OTHER INSTRUMENT offers all this for the price

- 98 White Light Stimuli in central 25 Field
- Colour Perimetry - for Toxic Retinopathy
- Macular Function Test
- Controlled Illumination
- Dark Adaptation - for Retinitis Pigmentosa
- Speed and ease of use
- Proven and published performance

1980 DESIGN AWARD · AN OUTSTANDING BRITISH PRODUCT · THE DESIGN COUNCIL



Clement Clarke International Ltd

Airmed House, Edinburgh Way, Harlow, Essex CM20 2ED

Tel 0279 414969   Tlx 81338   Fax 0279 635232

DID YOU TAKE YOUR DROPS?

What can you give a patien
as well a

Getting patients to comply with complicated dose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, the beta blocker most patients only need to take once a day.

This is possible because of Betagan's sustained activity over 24 hours,[1] which has been shown to be effective in controlling the int ocular pressure of up to 81% of patients on a once daily dose.[2]

Betagan offers new hope of improved co pliance for a whole range of glaucoma patier such as the elderly or arthritic, those with impaired vision, or those who live alone.

▼ **PRESCRIBING INFORMATION**
PRESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v).
ACTION: Beta-adrenergic blocking agent.
INDICATIONS: Reduction of intraocular pressure in chronic open-angle glaucoma and ocular hypertension.
CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS: Contra-indications: Bronchial asthma; history of bronchial asthma; chronic obstructive pulmonary disease; sinı bradycardia; second and third de atrioventricular block; cardiac failur cardiogenic shock; hypersensitivity to component. Caution in labile diabetes in patients receiving oral beta-adrene

who suffers from amnesia glaucoma?

What's more you also have the option of escribing Betagan at a twice daily dosage for ose patients who require additional control.
So next time you're looking for a simple t flexible treatment for open angle glaucoma, nsider Betagan.
It's a name worth remembering.

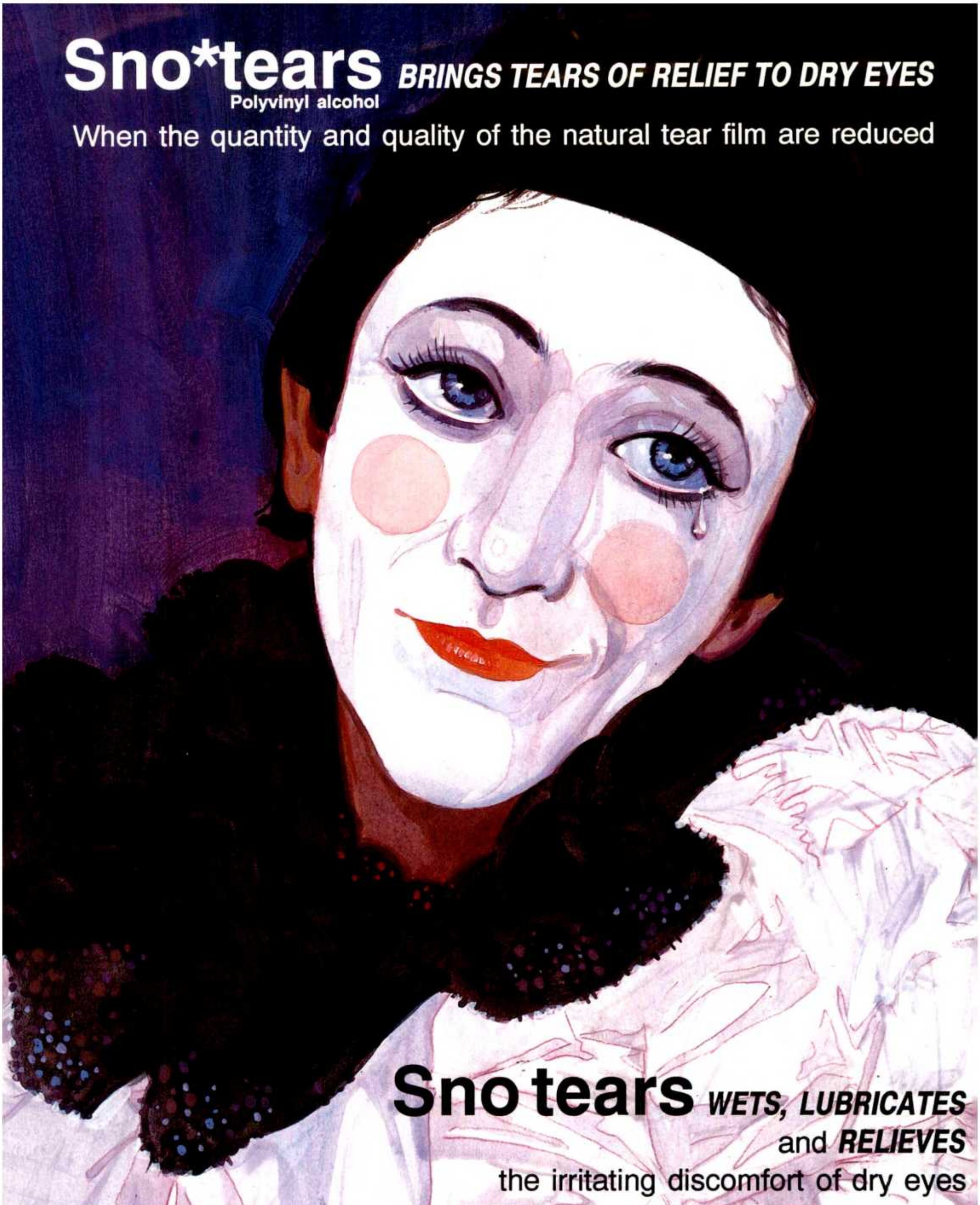
BETAGAN®
(levobunolol hydrochloride 0.5%)
ONCE DAILY
ONE DROP THEY WON'T FORGET

---

cking agents. Do not use in patients tinuing to wear hydrophilic (soft) tact lenses. Transient ocular burning stinging on instillation may occur. dycardia, hypotension, dyspnoea and ma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) once or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE: £5.05** PL 0426/0060. Full prescribing information is available on request.

1. Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11.

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.
® Betagan is a registered trade mark.


Sno*tears BRINGS TEARS OF RELIEF TO DRY EYES
Polyvinyl alcohol
When the quantity and quality of the natural tear film are reduced
Sno tears WETS, LUBRICATES and RELIEVES
the irritating discomfort of dry eyes

PRESCRIBING INFORMATION

● **Presentation**: Sno tears is a clear, colourless slightly viscous solution in a plastic dropper bottle. It contains polyvinyl alcohol 1.4% w/v together with benzalkonium chloride 0.004% w/v and disodium edetate 0.02% w/v as an antibacterial system. ● **Uses**: Sno tears is used topically to provide tear-like lubrication for the symptomatic relief of dry eyes and eye irritation associated with deficient tear production (usually in cases of keratoconjunctivitis sicca and xerophthalmia). Also used as an ocular lubricant for artificial eyes. ● **Dosage And Administration**: Adults, children and the elderly: The dose depends on the need for lubrication. Usually one or more drops as required or as prescribed. ● **Contra-indications**: Hypersensitivity to any component of the preparation. Contains benzalkonium chloride and should not be used when soft contact lenses are worn. ● **Other Undesirable Effects**: May cause transient mild stinging or temporarily blurred vision. ● **Warnings**: If irritation persists or worsens, discontinue use and consult a physician ● **Pharmaceutical Precautions**: Sno tears should be stored in a cool place. Sno tears, as with other eye drops, should be discarded one month after opening. ● **Legal Category**: P ● **Further Information**: Nil ● **Package Quantities**: Sno tears is supplied as a sterile ophthalmic solution in a 10ml plastic dropper bottle ● **Basic NHS Price**: £1.02 (April 1990) ● **Product Licence Number**: PL0033/0097

Smith & Nephew Pharmaceuticals Limited. Bampton Road, Harold Hill, Romford, Essex, RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

Smith+Nephew

*Trade Mark

British Journal of Ophthalmology, 1990, 74, 465–468

Ocular and visual defects in a geographically defined population of 2-year-old children

Maureen Stayte, Ann Johnson, Catherine Wortham

Abstract

Ocular and/or visual defects were diagnosed by age 2 years in 2·1% of infants born in 1984 in one health district. Infants of low birth weight or infants requiring special care in the neonatal period had a two and a half times greater risk of vision and ocular defects than the remainder of the population. In particular, the rate of squint and neurological disease affecting the visual system was significantly greater in this high risk group than in the low risk group. The degree of visual impairment in the high risk group tended to be more severe than in the low risk group. Overall, however, the majority of children with vision or ocular defects (85%) were in the low risk group.

With falling perinatal mortality the numbers of infants of low birth weight who survive the perinatal period are increasing.[1] These infants are known to be at increased risk of ocular and vision defects.[2,3] There is concern that they may be contributing unduly to pre-school vision impairment within the community. While Blind and Partially Sighted Registration is one source of severe visual impairment data, the information is often incomplete by 2 years of age and does not include all types of visual and ocular defects.

In order to look at this problem we have ascertained the outcome of referrals of infants from birth to 2 years to the hospital eye service in a geographically defined population. The numbers of referred infants who were of low birth weight or who had required special care in the neonatal period were compared with the number of referrals from the remainder of the population. The characteristics of the ocular and vision defects diagnosed in the two populations are described.

Materials and methods

Information on all infants who were referred for an ophthalmological opinion by 2 years of age was obtained by searching eye clinic and orthoptic records within Oxfordshire Health District. This was a manual search; only the Blind and Partially Sighted Registers were on a computerised system. It involved searching all hospital index files, hospital notes, and registers of new patients attending orthoptic departments within the Oxfordshire health district. Casualty records were excluded. Additional information was obtained from the paediatric assessment centres, from Special Needs Advisers to the Department of Education, Department of Social Services who held the 'Blind Register', Eye Operation Register, and the Birth Registers.

The following information was abstracted from the records: (*a*) Health district of birth; (*b*) birth weight; (*c*) whether admitted to special care nursery; (*d*) age at referral; (*e*) outcome of referral.

A case was defined as a child with a recognised or suspected ocular or visual abnormality requiring treatment or surveillance. Cases were classified as shown in Table I. Children with

TABLE I *Numbers of children with diagnosed ocular and vision defects at age 2 years*

					Number (rate/1000 survivors at 2 years)		
	High risk infants		*Low risk infants*		*Total infants**		*Relative (95% confidence limits)*
Heterotropia (intermittent or constant)							
(i) No glasses ordered	9	(35·8)	42	(13·3)	52	(14·6)	3·4 (1·7, 7·0)
(ii) Glasses ordered	5		41		46		1·9 (0·8, 4·9)
Defects associated with neurological disease (including optic atrophy and cortical blindness)	9	(23·0)	7	(1·1)	16	(2·4)	20·5 (7·7, 54·8)
Periorbital pathology (including anomalies of lid, orbit, and extraocular muscles)	–		13		13	(2·0)	–
Nystagmus:							
manifest	3	(7·7)	7	(1·3)	10	(1·7)	6·0 (1·6, 22·5)
latent	–		1		1		
Intraocular pathology (including retinopathy of prematurity)	1		9		10	(1·5)	1·8 (0·2, 14·0)
Refractive error without heterotropia (glasses ordered)	1		6		7		2·66 (0·3, 22·0)
Refractive error without heterotropia (no glasses ordered; surveillance and further refraction required)	1		5		6		3·2 (0·4, 27·3)
Esophoria without refractive error needing continued surveillance	–		6		6		–
Heterophoria with refractive error (glasses ordered)	–		3		3		–
Total number of infants* with vision or ocular defect	21	(53·7)	118	(18·9)	139	(21·0)	2·8 (1·8, 4·5)
Total number of infants in each group	391		6243		6634		

* Some infants have more than one defect

Oxford Eye Hospital, Walton Street, Oxford OX2 6AN
M Stayte
C Wortham

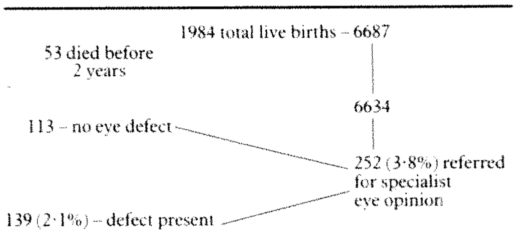
Oxford Region Child Development Project
A Johnson

Correspondence to:
Mrs M Stayte

Accepted for publication
15 February 1990

blocked tear ducts and conjunctivitis were excluded.

TABLE II *Total number of infants in study*


1984 total live births – 6687
53 died before 2 years
6634
113 – no eye defect
252 (3·8%) referred for specialist eye opinion
139 (2·1%) – defect present

The total population under study was divided into two groups:

(1) Infants born in 1984 to mothers resident in the Oxford health district at the time of birth, who were either less than 2000 g birth weight or who were 2000 g or more at birth and requiring admission to a special care nursery for longer than 24 hours were termed 'high risk'. These infants were identified as part of the Oxford Region Child Development Project[4] and were considered at increased risk of ocular and vision defect.

(2) Infants born in 1984 who were 2000 g or more at birth and did not require any special care in the neonatal period were designated as 'low risk'. This group consisted of infants with these characteristics who were resident in the district at age 2 years. While not all may have been born to mothers resident in Oxfordshire at the time of birth, it was assumed that among this low risk population the population movement into the district was balanced by those leaving the district.[5]

Outcome information was sought on infants from the high risk group who were known to have left the district and to have been referred for an ophthalmological opinion to a centre outside the district. Infants who had moved into the district after birth, and were known to have been of low birth weight or requiring special care were not included in the study.

Results

In 1984 there were 6687 live births to mothers who were resident in the Oxford health district at the time of delivery. Fifty three infants had died by age 2 years: 33 died in the neonatal period, a further 18 before the age of 1 year and two infants died in their second year (Table II). Forty two of the 53 infants who died were in the high risk group and 11 were in the low risk group. The mortality rate in the high risk groups was 97/1000 live births compared with a mortality rate of 1·8/1000 live births in the low risk population.

Of the 6634 infants alive at age 2 years 252 (3·8%) had been referred for an ophthalmological opinion. One hundred and thirty nine of these were diagnosed as having an ocular or visual defect. Overall 2·1% of the 2-year-old population had a diagnosed ocular or visual impairment.

Of these infants (alive at age 2 years) 391 were in the high risk group and 6243 in the low risk group (Table III). Twenty one of the 391 high risk infants and 118 of the 6243 low risk infants had an ocular or vision problem by age 2 years. Although the risk of such impairment was significantly higher in the high risk group than in the low risk group (relative risk=2·8 with 95% confidence limits of 1·8 to 4·5) (Fig 1), the high risk group contributed only 15% of all cases.

Overall the commonest defect was heterotropia, which was present in 70% of all children designated as cases (Table I). The types of heterotropia and heterophoria diagnosed by age 2 years are shown in Table IV. Approximately half the cases in each group had a constant esotropia, whereas only two children had constant exotropia. Heterophoria was recorded only in the low risk group. The risk of heterotropia was significantly greater in the high risk group than in the low risk group (relative risk= 2·7 with 95% confidence limits of 1·5 to 4·7).

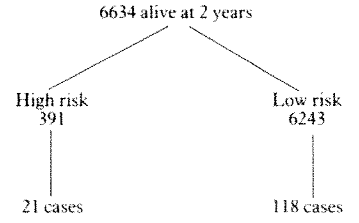
Ocular and visual defects associated with neurological disease accounted for 12% of all defects detected by age 2 years. Of the 16 infants in this category 11 had cerebral palsy. Six of these 11 children had a heterotropia. Many of the children with cerebral palsy had severe impairment of vision (three with optic atrophy and three with 'cortical blindness'). The relative risk of a vision/ocular defect associated with neurological disease in the high risk group of infants was 20·5 with confidence limits to 7·7 to 54·8.

Intraocular and periorbital pathology accounted for 17% of all cases, all but one of which were in the low risk group. The defects in the low risk group were lens opacities (2), congenital choroiditis (1), unilateral microphthalmos and coloboma (1), bilateral colobomata (1), correctopia (1), congenital toxoplasmosis (1), depigmented iris (1), cataract and retinal detachment secondary to trauma (1), unilateral ptosis (5), Marcus Gunn syndrome (2), Duane's syndrome (2; 1 type A, 1 type B), Brown's syndrome (1), and inferior oblique overaction, with binocular single vision in the primary position (3).

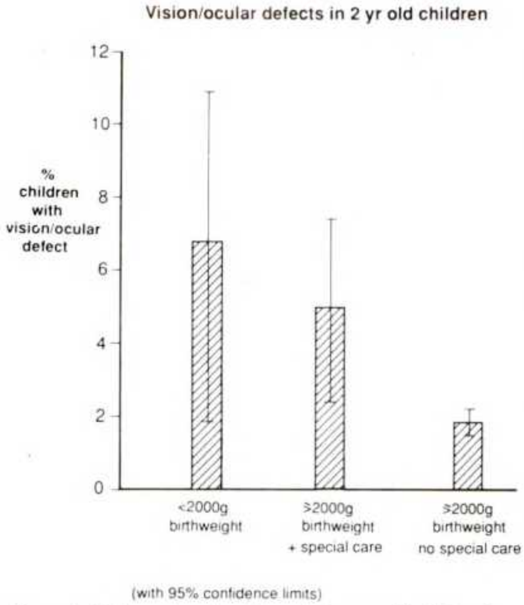
There was a single case of grade IV retinopathy of prematurity in the high risk group, classified under intraocular pathology.

The range of refractive errors are shown in Figure 2, showing the eye with the highest refractive error. Astigmatism is in minus cylinders. Seventy one children (51% of all children with an eye defect) had a recorded refractive error. Glasses were prescribed for 56 children. A further six children were not ordered glasses at this age but required further refractions and surveillance. No overall difference in the degree or type of refractive errors was found between the high risk and the low risk groups.

TABLE III *Numbers of infants in high risk and low risk groups*



Ten of the 139 2-year-old children with an eye defect were blind or had very low vision. The



(with 95% confidence limits)

Figure 1: Vision and ocular defects in 2-year-old children by birth weight group and by admission to special care nursery.

underlying causes were cortical blindness (3), optic atrophy (3) (all these six children had cerebral palsy), retinopathy of prematurity (1), toxoplasmosis (1), optic nerve hypoplasia (1), and leucodystrophy (1).

The proportion of children with visual defects who appeared to have no useful vision or who will require low vision aids was considerably greater in the high risk group than the low risk group (six of 21 in the high risk group compared with four of 118 in the low risk group). The relative risk of severe impairment in the high risk group was 30·0 with 95% confidence limits of 6·8 to 84·5.

Discussion

By age 2 years 3·8% of the infant population of a health district had been referred to a specialist eye service. A little over half of these referrals proved to fulfil the criteria of a case. Thus 2·1% of the population had a diagnosed ocular or visual defect by age 2 years, Kendal *et al* found 1·6% seen by 2 years,[6] rising to 8·9% at age 6 years, and Kohler looked at 4-year-olds and found 8·9%.[7]

The detailed search was unlikely to have missed cases referred within the health district. However, population movement and uneven shifts of population could result in underestimates in the numbers of cases in the low risk population. Ascertainment was more likely to be complete in the high risk group, where there was a vigorous follow-up, including tracing infants who had moved outside the district. Underascertainment could also occur as a result of failure of cases to come to the attention of the ophthalmological services by age 2 years. This was again more likely to occur in the low risk group, where surveillance was less rigorous. However, despite this possible underestimate of the numbers of cases in the low risk group, 85% of all cases were from this section of the population.

TABLE IV *Types of strabismus diagnosed by age 2 years*

	Total number of cases	*High risk infants*	*Low risk infants*
Heterotropia			
Constant:			
convergent	60	10	50
divergent	2	1	1
Intermittent:			
divergent	22	2	20
convergent	14	2	12
Total	98	15	83
Heterophoria			
Esophoria	8	0	8
Exophoria	1	0	1
Total	9	0	9
Total number of infants in each group	6634	391	6243

We confirmed the previously described increase in risk of ocular and vision defects among low birth weight infants and infants requiring special care.[2,3,8] In our series this high risk group had a higher rate of heterotropia, a higher prevalence of ocular and vision defects associated with neurological deficit, and a more severe level of visual loss.

The prevalence of heterotropia in the population studied was 1·5%, comparable with 1·3% described by Friedman *et al*[9]; esotropia comprised 1·0% of cases. Few cases of heterophoria were detected. This could be because they cause little concern in this age group. Further study of this population may show a higher percentage of these cases. The small numbers of cases of intermittent esotropia may be due to the fact that the accommodative system is not fully functional in many children by 2 years of age.[10] All cases of intermittent exotropia of divergence excess type may not have been detected, as most fixation tasks are carried out at near fixation in this age group.

In a recent study of vision screening tests applied by health visitors to high risk infants under the age of 2 years almost all the children who were identified as having a heterotropia had an obvious defect on direct observation.[11]

Low birth weight infants and infants admitted to a special care nursery have a higher prevalence of cerebral palsy than the remainder of the infant population.[12] Eye defects are frequently present in children with cerebral palsy,[13] and indeed such defects accounted for almost half of all eye defects seen in the high risk group. Eye examination of all children with a central motor deficit would appear to be indicated. Conversely, the presence of a heterotropia in a low birth weight infant may be a marker of an underlying motor deficit.

Amblyopia was not included in our classification of defects, as the diagnosis could not be confidently made in this very young age group.[14] Accurate testing of uniocular visual acuity was not possible before the age of 2 years with the equipment available in the clinics. However, a number of children with strabismus and anisometropia as well as those with conditions such as lens opacities and ptosis, were under observation, or receiving treatment for potential or suspected amblyopia. They are classified within other groups as appropriate.

At the time of this study there was no systematic ophthalmological follow-up exam-

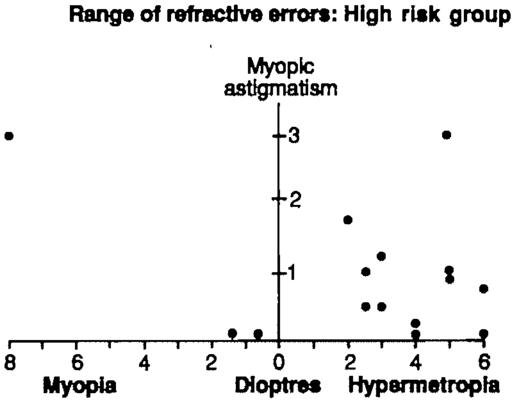


Figure 2A

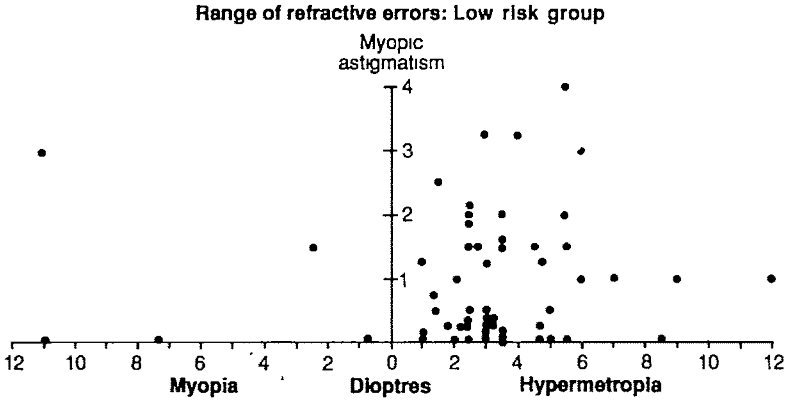


Figure 2B

Figure 2. Range of refractive errors in high risk and low risk groups. (Eye with highest refractive error recorded).

ination of infants who had been in the Special Care Baby Unit, and hence milder grades of retinopathy of prematurity were not consistently reported. A system of regular evaluation of all such infants is now operating, and it is likely that this will result in an increase in the number of high risk infants requiring ongoing surveillance by specialist ophthalmological services.

Not all children had a recorded refractive error, but the overall impression was that the range of refractive errors did not differ between the high risk and low risk groups. In particular we were unable to demonstrate a high prevalence of myopia (possibly as a feature of retinopathy of prematurity) in the low birth weight population as has been previously described.[8 13] However, without a systematic follow-up of the ocular status of the low birth weight infants it is likely that some children with myopia will only become known to the ophthalmological services after the age of 2 years.

Overall, we conclude that, although the relative risk of ocular or visual impairment is high in infants who have been of low birth weight or been admitted to a special care nursery, these infants will form only a small proportion of all defects seen by the ophthalmic services by the age of 2 years. Yet their disability is often severe and associated with other deficits especially in the motor area. Hence the demands they make on clinical services are considerable.

It is possible that in future the numbers of impaired infants in the high risk group may increase. It is likely that, with neonatal intensive care, mortality rate among the high risk infants will continue to fall, and it is arguable that as more of the vulnerable high risk infants survive the numbers of children with a vision or ocular defect will increase. A counter-argument is that the increasing sophistication of neonatal intensive care will in the future result in not only a continuing fall in mortality rate but also an improving quality of survivors. These two opposing views are at present largely unsubstantiated, and as the limits of viability continue to be lowered it will be essential to monitor trends in numbers and characteristics of ocular and visual defects seen in the early childhood population.

We thank Ms Alison Macfarlane for statistical advice, and Miss Rosemary King and Mrs Olive Goddard for help with preparation of the manuscript.

We are grateful to the staff of orthoptic clinics, especially in Horton General Hospital, Banbury and Wallingford Community Hospital, and the staff of medical records departments throughout the district, for their assistance with this study.

Funds for this study were provided by Oxfordshire Health Authority (Locally Organised Research Grant). The Oxford Region Child Development Project is funded jointly by the Department of Health and the Oxford Regional Health Authority

1 Macfarlane A, Mugford M *Birth counts Statistics of pregnancy and childbirth* London: HMSO, 1984.
2 Hungerford J, Stewart A, Hope P. Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage. *Br J Ophthalmol* 1986, 70: 463–8.
3 Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight *Br J Ophthalmol* 1983, 67: 302–5
4 Johnson A. Screening tests for hearing and vision impairment. How and when are they done? *Health Visitor* 1986, 59: 140–2
5 Office of Population Censuses and Surveys *Key population and vital statistics*. Series VS 15, no. 11. London HMSO, 1988
6 Kendall JA, Stayte MA, Wortham C. Ocular defects in children from birth to 6 years of age. *Br Orthopt J* 1989; 46: 3–6
7 Kohler L. Health control of 4 year old children An epidemiological study of child health *Acta Paediatr Scand (Suppl)* 1973; 62: 17.
8 Kushner BJ Strabismus and amblyopia associated with regressed retinopathy of prematurity. *Arch Ophthalmol* 1982, 100: 256–61.
9 Friedman Z, Neumann E, Hyams SW, Peleg B. Ophthalmic screening of 38 000 children, age 1 to 2½ years, in child welfare clinics *J Pediatr Ophthalmol Strabismus* 1980; 17: 261–7
10 Burian HM, Von Noordon GK. *Binocular vision and ocular motility* 3rd ed St Louis: Mosby, 1985: 5: 92
11 Johnson A, Stayte MA, Wortham C. Vision screening at age 8 months and 18 months *Br Med J* 1989; 299: 545–9.
12 Johnson A, King R A regional register of early childhood impairments – a discussion paper. *Community Med* 1989; 11: 352–63.
13 Black P Visual disorders associated with cerebral palsy. *Br J Ophthalmol* 1982, 66: 46–52.
14 Shaw DE, Minshull C, Fielder AR, Rosenthal AR Amblyopia – factors influencing age of presentation *Lancet* 1988, ii: 207–9.

For those patients who should avoid taking nonselective ocular beta blockers...

“Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”[1]

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

A bright outlook for glaucoma patients

For effective control of IOP minimising the risks associated with nonselective beta-blockade [2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only ß₁ selective ocular beta blocker

SELECTIVE β1 BETA-BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased corne sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have bee reported. Systemic reactions following topical administration of Betoptic (eg. insomnia and depressiv neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies hav not demonstrated any specific hazard there are no adequate and well-controlled studies in pregna women. Because animal studies are not always predictive of human response this drug should be use during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known whethe Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is admin stere to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed fro the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml droptainer. **PRODUCT LICENC HOLDER AND NUMBER:** Alcon Laboratories U.K. 0649/0097. DATE OF PREPARATION: JANUARY 19

Further information is available on request.

Alcon

SPECIALISTS IN EYE CARE

Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

REFERENCES:
1. Jones FL, Ekberg NL. Letter N Eng J Med 1979; **301**: 270.
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62.
3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92.
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

British Journal of Ophthalmology, 1990, 74, 469–471

Conjunctival biopsy in the diagnosis of sarcoidosis

Richard F Spaide, David L Ward

Abstract

We prospectively studied 47 sarcoidosis suspects and compared conjunctival and transbronchial lung biopsies in these patients. Thirty-four patients had positive findings on biopsy by either method. The transbronchial biopsy was positive in 31 patients, and the conjunctival was positive in 19. The transbronchial lung biopsy was more likely to be positive in black patients ($p=0\cdot009$) and in patients with pulmonary infiltrates on chest *x* ray ($p=0\cdot0044$). In comparison, the conjunctival biopsy was more likely to be positive in patients with conjunctival follicles ($p=0\cdot036$), ocular abnormalities consistent with sarcoidosis ($p=0\cdot02$), and in patients with pulmonary infiltrates on chest *x* ray ($p=0\cdot029$). Iritis was present in 12 patients, enlarged lacrimal glands in three, and vitritis in five. We conclude that the conjunctival biopsy is an effective means of diagnosing sarcoidosis and that every sarcoidosis patient should have an ophthalmic examination.

Sarcoidosis is a granulomatous disorder of multiple organ systems that has no known cause, has an unpredictable course, and can mimic many other diseases. It is predominantly found in young adults, who frequently have bilateral hilar adenopathy, pulmonary infiltration, respiratory problems, skin lesions, and ocular problems.[1-7] The diagnosis of sarcoidosis is best supported when histological evidence supports the clinical and radiological findings.[1]

The granulomas are usually widely distributed, so the biopsy site should be determined by the risks versus the likelihood of success. Transbronchial lung biopsy (TBBX) by a flexible fibreoptic bronchoscope is currently the biopsy procedure of choice in making the diagnosis of sarcoidosis.[8 9] However, conjunctival biopsy (CBX) has frequently been reported to be a simple procedure that is helpful.[10-17] We conducted a prospective study of transbronchial and conjunctival biopsies in 47 patients suspected of having sarcoidosis on clinical grounds, and compared the rates of positive biopsy results for the two procedures. We also catalogued the ocular findings to determine the incidence of ocular abnormalities in newly diagnosed sarcoidosis patients.

Patients and methods

This study was performed at a medical centre serving both local and referred patients. We considered any patient who had symptoms or findings suggesting a differential diagnosis that included sarcoidosis to be a sarcoidosis suspect. We used the definition of sarcoidosis from the Seventh International Conference on Sarcoidosis[1] as our case definition. During the study period 49 consecutive patients met the entrance criteria of sarcoidosis as a differential diagnosis. The nature and purpose of the biopsy procedures were explained to the patients, who gave written informed consent. Two patients chose not to participate in the study; this report is on the remaining 47.

All patients had skin testing with intermediate purified protein derivative of tuberculin (PPD) and an anergy panel, and none of these patients had a positive reaction to the tuberculin antigen. Each patient had chest *x* rays, and these *x* rays were graded into four stages according to conventional methods.[18] Stage 0 is normal, and stage 1 has bilateral hilar adenopathy. Stage 2 has enlarged hilar nodes with pulmonary opacities, and stage 3 has pulmonary infiltrates without node enlargement. Every patient had function tests (PFT). For our analysis we examined the forced vital capacity, forced expiratory volume in 1 second, forced expiratory flow, 25–75% maximum voluntary ventilation, and total lung capacity. Each subtest was considered abnormal if it was less than 75% of the predicted value for patients the same age, sex and size.

Each sarcoidosis suspect was examined by a chest specialist, who obtained at least six and usually eight to 10 random transbronchial biopsies from each patient with a fibreoptic bronchoscope. We obtained angiotensin converting enzyme (ACE) levels in 29 patients. Every patient had a complete ocular examination by an ophthalmologist. A strip of conjunctiva 10 to 12 mm long was excised from each eye, and any conjunctival abnormality noted on slit-lamp examination was included in the biopsy when possible. The biopsy specimens were fixed in formalin and embedded in paraffin blocks, were sectioned (Fig 1), and stained with haematoxylin and eosin. If a biopsy showed non-caseating granulomas, it was stained for fungal and acid fast organisms. If no organisms were present, the biopsy was considered to be positive for sarcoidosis (Fig 2).

History, physical and ocular findings, PFT results, ACE levels, chest *x* ray stage, and biopsy findings of the 47 patients were entered on to a form adapted for use with a computer database. The data were evaluated with the help of descriptive statistics and, for frequency data, Fisher's exact test of probability. For analysis the chest *x* ray staging was divided into two groups. Stages 0 and 1 chest *x* rays were grouped together and called pulmonary infiltrate negative; stages 2 and 3 were group together and called infiltrate positive. We classified chest *x* ray results in this manner because our sample size was small and also chest *x* ray stages in sarcoidosis are not strictly ordinal,[18] so that making four strata for the *x* rays violates the assumptions in the statistical methods used. We rejected the null

Ophthalmology Service, Landstuhl Army Regional Medical Center, and Manhattan Eye, Ear and Throat Hospital, New York, USA
R F Spaide

Epidemiology Section, 10th Medical Laboratory, Landstuhl Army Regional Medical Center, Landstuhl, West Germany
D L Ward

Correspondence to:
Richard F Spaide, MD,
Manhattan Eye, Ear and
Throat Hospital, 210 East
64th Street, New York,
NY 10021, USA.

Accepted for publication
20 February 1990

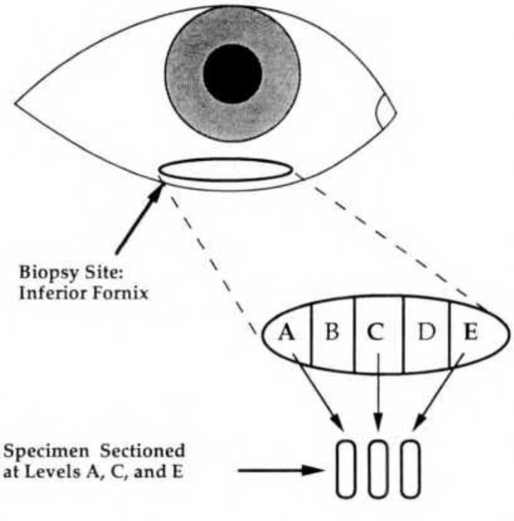


Figure 1: The conjunctival biopsy was taken from the inferior fornix. The specimen was sectioned at three levels for histopathologic evaluation.

hypothesis if the probability of committing a type I error was 0·05 or less.

Results

Of the 47 patients studied 31 were male (24 blacks, 7 Caucasians) and 16 female (11 blacks, 5 Caucasians). The mean age was 29·4 years (SD 6·2 years), while the average duration of symptoms was 6·2 months (SD 9·1 months). There was no statistically significant difference in age or duration of symptoms among males and females or Caucasians and blacks.

Conjunctival follicles were found in 12 patients. Three patients had enlarged lacrimal glands. Iritis was present in 12 patients (25·5%), keratic precipitates were present in 4 (8·5%). Five patients (10·6%) had anterior vitritis, with four of these having snowballs in the vitreous. All patients with intraocular inflammation were black (p=0·016). Any ocular abnormality consistent with sarcoidosis – that is, conjunctival follicles, enlarged lacrimal glands, or intraocular inflammation – was found in 20 patients, and 18 were black.

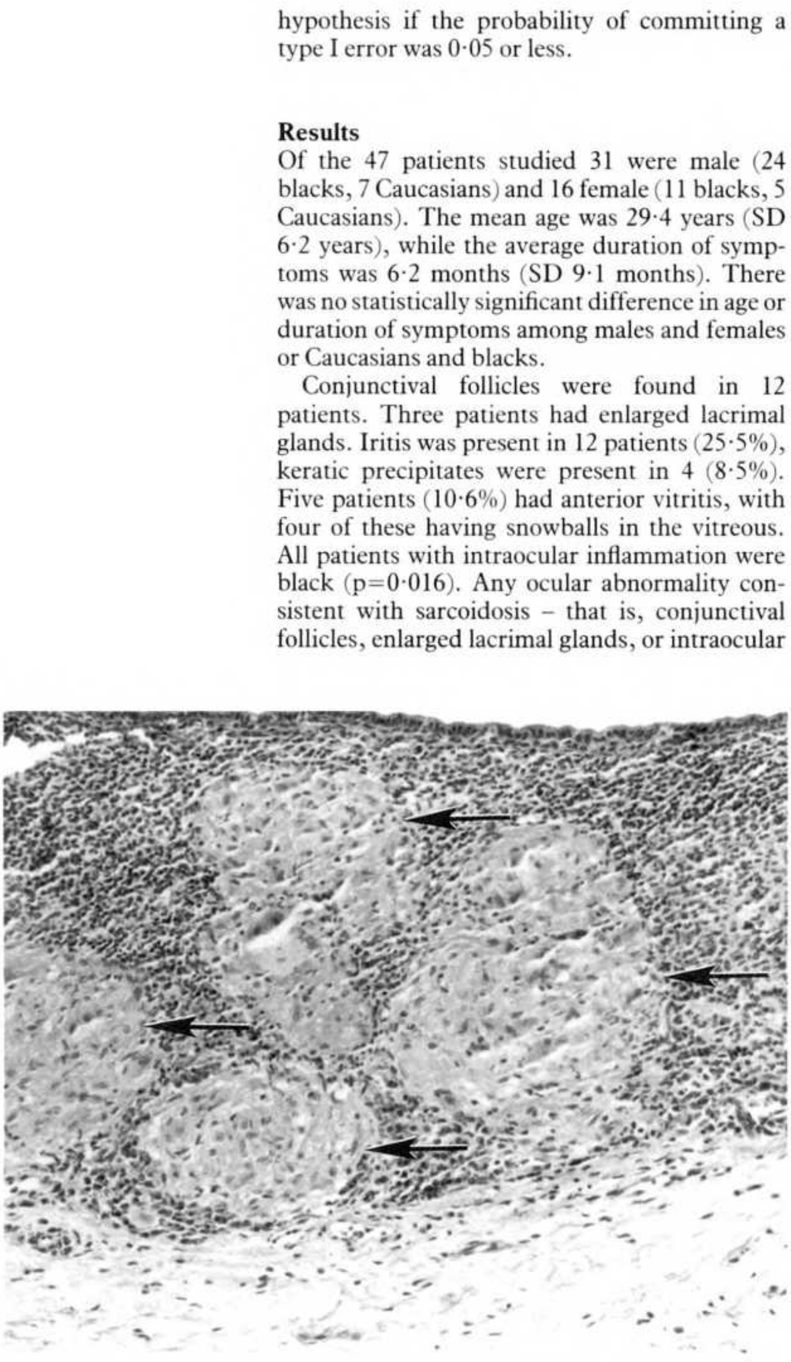


Figure 2: Photomicrograph of a conjunctival biopsy with arrows showing individual non-caseating granulomas. (Haematoxylin and eosin × 120.)

Of the 47 patients 31 (66%) had a positive transbronchial biopsy and 19 (40·4%) had a positive conjunctival biopsy. A total of 34 were discovered to have sarcoidosis by one or both of these two biopsy methods. Of the 13 patients who did not have a positive TBBX or CBX one had a lymph node biopsy positive for sarcoidosis; four patients had additional lung biopsies, one of which was positive; one patient with asymmetrical hilar adenopathy had two non-diagnostic TBBX procedures, and he was discovered to have sarcoidosis by mediastinoscopy; one patient was lost to follow-up; the remaining patients, including one who had a stable chest *x* ray for seven years, were followed up without any additional biopsies. Thirty-seven patients were eventually found to have histological evidence of sarcoidosis of whom conjunctival biopsy discovered 51% and transbronchial lung biopsy 84%.

Transbronchial biopsies were positive in 77·1% and conjunctival biopsies in 45·7% of black sarcoidosis suspects. Caucasian sarcoidosis suspects had 33·3% and 25% positive TBBX and CBX respectively. The difference between the two races was significant for the TBBX (p=0·009) but not for the conjunctival biopsy (p=0·18). Patients with pulmonary infiltrates had a positive TBBX 80·6% of the time, while 37·5% of patients with no pulmonary infiltrates had a positive biopsy (p=0·0044). Likewise, the conjunctival biopsy was more likely to be positive in patients with pulmonary infiltrates than patients without infiltrates, 51·6% versus 23·1% (p=0·029). Conjunctival biopsies were positive more often in sarcoidosis suspects with follicles, 66·7%, than those with a normal conjunctiva 31·4% (p=0·036). Conjunctival biopsies were positive in 60% of those with any eye abnormality consistent with sarcoidosis compared with 25·9% of those with no abnormalities on ocular examination (p=0·02). We could find no element of the PFT, singly or in combination, that correlated with a positive TBBX or CBX.

The diagnosis of sarcoidosis was established in 10 of the 12 suspects with conjunctival follicles, and the conjunctival biopsy detected 8 (80%) of these. Any ocular abnormality consistent with sarcoidosis was found in 20, and 18 were eventually found to have sarcoidosis. The conjunctival biopsy detected 12 of these (66%).

The ACE test was abnormal in 62% of those with positive biopsies. Black patients, patients with intraocular inflammation, or patients with more advanced chest *x* ray stages were not more likely to have an abnormal ACE test.

Discussion

More than one-half of the sarcoidosis patients (54·1%) had some type of ocular abnormality, and 32·4% had intraocular inflammation. These values are greater than in previous studies being 34% and 28% respectively. The previous investigations were retrospective studies from sarcoidosis centres, and it was difficult to determine if the patients were being treated for sarcoidosis at the time of their ocular examination. We performed a prospective study of untreated patients. All our patients were examined by an ophthalmologist in contrast to some of the studies where only selected patients were examined by an ophthalmologist. Because of our findings we would strongly recommend early ophthalmic consultation for every sarcoidosis patient.

The conjunctival biopsy was positive in 40·4% of suspects. Again, this number is hard to compare with previous reports. Past studies frequently included patients with known sarcoidosis, included biopsies only in patients with[13] or without[17] conjunctival abnormalities, and had large variations of the biopsy size.[11] Our biopsy size was consistent from patient to patient and larger than in many of the studies. In past studies the range of positive conjunctival biopsies ranged from 0 to 75%, with a weighted average of 24%. In our study conjunctival biopsies were positive in 66·7% with and 31·4% without conjunctival follicles. Thus we found blind biopsies can be useful in the diagnosis of sarcoidosis, which is in contrast to previous studies that have reported blind conjunctival biopsies being valueless.[14,19]

Although our study did not have any control patients, three previous studies have addressed the incidence of false positive conjunctival biopsies.[11,12,14] The total number of control conjunctival biopsies in these three studies was 116, and many of these patients had other granulomatous disorders. There were no false positives. In our study and in the previous studies,[10-17] no serious complications have been reported from conjunctival biopsy.

Angiotensin converting enzyme has been used to help make the diagnosis of sarcoidosis, but there are two problems with using the ACE test. The first is its low sensitivity. The second is that every disease that would be included in a differential diagnosis with sarcoidosis can also cause a rise in ACE levels.[23,24] Although the histological picture of sarcoidosis – non-caseating granulomas – is not pathognomonic, histopathological examination of tissue provides information that helps to discriminate between the elements in the differential diagnosis of sarcoidosis, something the ACE test does not do efficiently.

We found biopsy of the conjunctiva to be an effective and useful method of obtaining this histopathological information, and it seemed particularly worthwhile in patients with advanced chest *x* ray stages or ocular abnormalities. Transbronchial lung biopsy is expensive and invasive, and carries a greater risk of serious complication than conjunctival biopsy. A practical biopsy strategy would be to biopsy the conjunctiva of sarcoidosis suspects and, only if the conjunctival biopsy is negative, do a transbronchial lung biopsy. Limiting the conjunctival biopsy to those patients with ocular abnormalities or advanced chest *x* ray stages might prove to be even more cost effective.

The members of the Pulmonary Service, Dr David Russell, Dr David Goya, and Dr Freddie Negron performed the transbronchial biopsies on the patients in this study

This work was supported in part by LuEsther T Mertz Retinal Research Fund, Manhattan Eye, Ear and Throat Hospital, New York.

1 James DG, Turiaf J, Hosada Y, *et al* Description of sarcoidosis: report of the subcommittee on classification and definition *Ann NY Acad Sci* 1976; **278**: 742
2 Jabs DA, Johns CJ Ocular involvement in chronic sarcoidosis *Am J Ophthalmol* 1986; **102**: 297–301.
3 Obenauf CD, Shaw HE, Sydnor CF, Klintworth GK Sarcoidosis and its ophthalmic manifestations *Am J Ophthalmol* 1978; **86**: 648–55
4 Iwata K, Nanba K, Sobue K, Abe H Ocular sarcoidosis: evaluation of intraocular findings. *Ann NY Acad Sci* 1976, **278**: 445–54.
5 James DG. Ocular sarcoidosis *Ann NY Acad Sci* 1986, **465**; 551–63.
6 Crick RP, Hoyle C, Smellie H The eyes in sarcoidosis. *Br J Ophthalmol* 1961; **45**: 461–81
7 Dresner MS, Brecher R, Henkind P. Ophthalmology consultation in the diagnosis and treatment of sarcoidosis *Arch Intern Med* 1986; **146**: 301–4.
8 Daniel TM Sarcoidosis. In: Baum GL, Wolinsky E, eds *Textbook of pulmonary diseases* Boston Little Brown, 1983 685–701.
9 Daniele RP. Sarcoidosis: diagnosis and management. *Hosp Prac (Off)* 1983, **18**: 113–22.
10 Karcioglu ZA, Brear R. Conjunctival biopsy in sarcoidosis *Am J Ophthalmol* 1985; **99**: 68–73.
11 Khan F, Wessely Z, Chazin SR, Seriff NS. Conjunctival biopsy in sarcoidosis: a simple, safe, and specific diagnostic procedure *Ann Ophthalmol* 1977, **9**: 671–6.
12 Bornstein JS, Frank MI, Radner DB. Conjunctival biopsy in the diagnosis of sarcoidosis. *N Engl J Med* 1962, **267**: 60–4.
13 Solomon DA, Horn BR, Byrd RB, Lorfel RS, Griggs GA The diagnosis of sarcoidosis by conjunctival biopsy *Chest* 1978, **74**: 271–3.
14 Crick R, Hoyle C, Mather G Conjunctival biopsy in sarcoidosis. *Br Med J* 1961, ii. 1180–1
15 Karma A, Sutinen S, Karma P Conjunctival and tonsillar biopsies in sarcoidosis. *Chest* 1980; **78**: 900–1.
16 Merritt JC, Lipper SL, Peiffer RL, Hale LM Conjunctival biopsy in sarcoidosis. *J Natl Med Assoc* 1980; **72**: 347–9
17 Nichols CW, Eagle RC, Yanoff M, Menocal NG Conjunctival biopsy as an aid in the evaluation of the patient with sarcoidosis. *Ophthalmology* 1980; **87**: 287–91
18 DeRemee RA The roentgenographic staging of sarcoidosis Historic and contemporary perspectives *Chest* 1983, **83**. 128–33.
19 James DG. Ocular sarcoidosis *Am J Med* 1959, **26**. 331–9
20 Gronhagen-Riska C, Serlos O, Wagar G, Fyhrquisf Angiotensin converting enzyme II Serum activity in early and newly diagnosed sarcoidosis. *Scand J Resp Dis* 1979, **60**: 94–101
21 Romer FK, Angiotensin-converting enzyme in newly detected sarcoidosis with special reference to enzyme levels in patients with erythema nodosum *Acta Med Scand* 1980, **208**: 437–43.
22 Rizzato G, Blasi A A European survey on the usefulness of “GA lung scans in assessing sarcoidosis Experience in 14 research centers in seven different counties *Ann NY Acad Sci* 1986; **465**: 463–78
23 Studdy PR, Lapworth R, Bird R Angiotensin converting enzyme and its clinical significance – a review *J Clin Pathol* 1983; **36**: 938–47
24 Gronhagen-Riska C. Angiotensin converting enzyme I Activity and correlation with serum lysozyme in sarcoidosis, other chest or lymph node diseases and healthy persons *Scand J Resp Dis* 1979; **60**: 83–93

British Journal of Ophthalmology, 1990, 74, 472–476

Changes in waveform of congenital nystagmus associated with biofeedback treatment

Mikako Mezawa, Satoshi Ishikawa, Kazuhiko Ukai

Abstract

A study was made of the parameters of congenital nystagmus which responded to auditory biofeedback treatment. The parameters studied included foveation time, amplitude, and frequency. The patient's right retina was observed with an infrared television fundus camera, and the fundus image was recorded on video tape. The position of the eye during nystagmus, observed via the fundus camera and recorded on video, was analysed at every 1/60 second intervals. The displacement in degrees between the fixation target, projected on to the retina, and the foveola was measured for each interval. Using biofeedback, the subjects could voluntarily suppress nystagmus and prolong foveation time. A damping of the nystagmus amplitude, intensity, and frequency was observed. On the average the intensity decreased by about 40%, and the foveation time was prolonged by about 190%. After completion of the training all the patients reported a subjective improvement in their vision when suppressing their nystagmus. Possibly biofeedback training acts to reduce the nystagmus and extend foveation time, thereby improving the ability to fixate.

Department of Ophthalmology, School of Medicine, Kitasato University, Sagamihara, Kanagawa, Japan
M Mezawa
S Ishikawa
K Ukai

Correspondence to
Satoshi Ishikawa, MD,
Department of Ophthalmology, School of Medicine, Kitasato University, 1–15–1 Kitasato, Sagamihara, Kanagawa 228, Japan

Accepted for publication
1 March 1990

Non-surgical treatment of congenital nystagmus has included prism treatment[1] as well as drug treatment.[2,3] Recently an auditory biofeedback method, as well as acupuncture, was introduced.[4-7] Well trained patients can damp their nystagmus by using acoustic signals generated from the eye movements. Following training some patients could deliberately suppress their nystagmus even without the use of auditory equipment. However, the reason for the effective damping of nystagmus by this method remains unclear. To understand this effect better it is important to compare waveform and foveation time before and after suppression of nystagmus.

Classifications of congenital nystagmus waveforms have been studied.[8,9] However, the change in waveform by biofeedback training has not been studied. Direct observation of the fovea is absolutely essential to analysing these changes, especially changes in the foveation time. To accomplish this we used an infrared television camera with a built-in fixation target. Time sequence fundus photography was performed every 1/60 second (16·7 ms) and was analysed by an image analyser tied into a computer system. In particular the relationship between the position of the foveola and the projected fixation target on the retina was measured. Changes in the foveation time as well as in the waveform were thus demonstrated.

Table 1 Status summary for each patient

Case	Age	Sex	*Corrected vision* Right	*Corrected vision* Left	*Null point location (degrees)*	*Waveform prior to voluntary suppression*	*Result of voluntary suppression*
1	20	F	20/20	20/20	0	Jerk with extended foveation	Excellent
2	17	F	20/20	20/20	Left 5	Dual jerk	Excellent
3	18	M	20/20	20/20	0	Jerk with extended foveation	Excellent
4	13	F	20/40	20/30	Left 10	Pure jerk	Fair
5	13	M	20/30	20/30	Left 10	Pseudopendular with saccades	Excellent
6	17	M	20/50	20/70	0	Pendular with foveating saccades	Fair
7	7	M	20/100	20/100	0	Pendular with foveating saccades	Poor

Materials and methods

PATIENTS

Seven patients between the ages of 7 and 20 (mean 15) were studied. All had horizontal congenital nystagmus. Table I summarises the status of the patients and the results of biofeedback therapy. Four cases (nos 1, 2, 3, 4) were of the jerk type while the others (nos 5, 6, 7) were either pendular or pseudopendular types of nystagmus. Apart from nystagmus no other ocular anomaly was present. We have also examined for and excluded the presence of albinism or partial variants of it and of optic nerve hypoplasia. In cases 1, 3, 6, and 7 the null point was located in the primary position, while in cases 2, 4, and 5 the null points were located to the left 5°, 10°, and 10° respectively. Each patient participated in auditory biofeedback therapy for the suppression of the nystagmus five or six times over a six-month period. This method has been mentioned elsewhere.[6] Convergence training was used with an associated increase in the tonus of frontal, orbicular, abdominal, diaphragmatic, or throat muscles.

During the biofeedback treatment eye movements were recorded by a limbus tracking device (photoelectric oculography with a bandwidth of 100 Hz). After being trained most patients could control their nystagmus partly and in some cases completely, even without the auditory feedback equipment. In cases 1, 2, 5, and 7 the damping of nystagmus was associated with changes in lid muscle tonicity, while cases 3, 4, and 6 associated a damped nystagmus with changes in tonicity of the diaphragm and abdominal muscles.

OBSERVATION OF NYSTAGMUS FROM THE FUNDUS

The retina was observed with an infrared television fundus camera with and without voluntary suppression. Its assembly and this method have

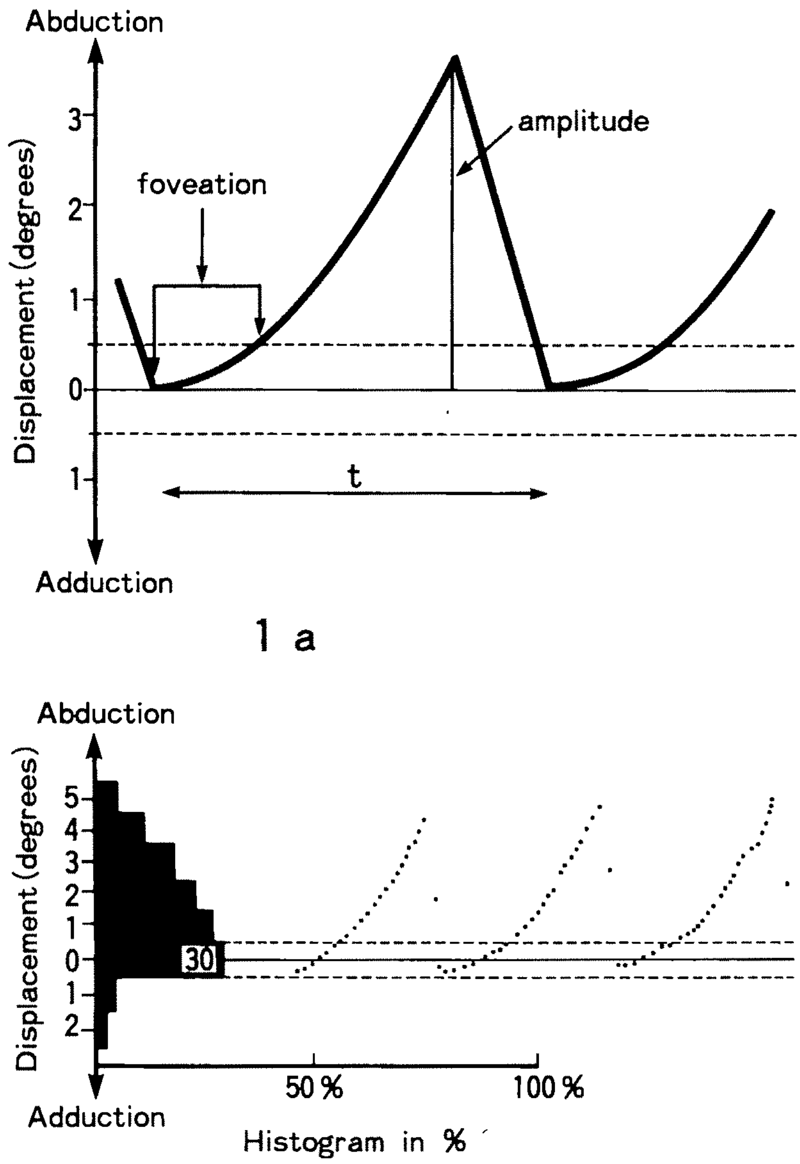


Figure 1 Waveform analysis (schematic drawing). a: *Determination of foveation indicated by two vertical arrows. Amplitude and frequency (1/t) are measured as shown. The zero axis indicates the foveola with a dotted line 0·5° to either horizontal directions defining the central foveal zone.* b: *Actual plot of a nystagmus waveform. Only the first three waves are shown. Each dot in the waveform corresponds to a 1/60 second video picture. The number of dots within each one degree zone surrounding the central foveal zone was tallied and plotted in the histogram to the left. The number 30 at the centre of the histogram indicates the maximum dot density within a 1° zone as a percentage of total.*

been described previously by Tani.[10] The patient was asked to fixate a target of 2′ in visual angle which was set inside the infrared television fundus camera. The right eye was used in all cases. The image of the fundus and the position of the fixation target over time were recorded by the videotape recorder. The position of two specific retinal points, such as the crossing of two vessels or a vessel crossing the disc margin, was measured in each 1/60 second time sequence picture over a 10 second period for each case. We thus obtained a total of 600 points of postion data from the fundus picture recordings of each eye, which were then converted into nystagmus waveforms to show the position of the foveola with regard to the fixation target over time. The average error as indicated by standard deviation was less than 3′ of arc. Using this method and by analysing each waveform in this way, we could establish the status of foveal fixation in each case.

ANALYSIS

For each case the nystagmus was classified according to the waveform obtained by the above method. We also analysed amplitude, frequency, intensity (amplitude×frequency), and foveation time. In addition the analysis of eye positions expressed as a percentage rate was shown by histogram. For the purposes of analysis the fixation target was considered to be at the zero point, and the ordinates indicate the eye position. As shown in Figure 1a, a zone of 0·5° (temporal and nasal) from the target was chosen as the central zone for foveal fixation. Foveation time is taken as the amount of time spent by the eye position within this zone and is indicated in this example by the horizontal distance between the two arrows. Note that the wave portion where the eye crossed into the central zone, corresponding to the quick phase of nystagmus, was not included in the calculation of foveation time. Foveation time was recorded in milliseconds. A histogram was made showing the breakdown of time spent by the eye (that is the number of dots) as a percentage rate, in the central foveal zone as well as for other 1° zones extending nasally and temporally out from the fovea. In the example in Figure 1b, as well as in most of the cases, the maximum percentage on the histogram corresponds with central fixation. The number above the histogram peak indicates this percentage rate.

Results

CHANGE IN WAVEFORM WITH VOLUNTARY SUPPRESSION

The waveforms (Fig 2) and the histograms (Fig 3) obtained from the seven cases are shown. Case 1 had leftward jerk nystagmus with extended foveation. Without voluntary suppression (A) the eye moved away from the target during the slow phase, and foveation, indicated by arrows, occurred at the termination of the quick phase. With voluntary suppression (B) nystagmus was reduced and excellent foveation was seen. In Figure 3 the histogram shows that the central foveal zone has the largest percentage of time, improving significantly from 32% to 76% with voluntary suppression.

Case 2 had a rightward jerky nystagmus. Without voluntary suppression the eye moved away from the foveola during the fast phase, and foveation occurred during the slow eye movements. With voluntary suppression excellent foveation was seen with some small occasional flicks, possibly a physiological form of nystagmus. The histogram maximum percentage significantly improved from 36% to 82% with voluntary suppression.

Case 3 had leftward jerk nystagmus with extended foveation. The foveation is shown by arrows and the waveform changed from a unidirectional type to a bidirectional type jerk nystagmus with voluntary suppression. The his-

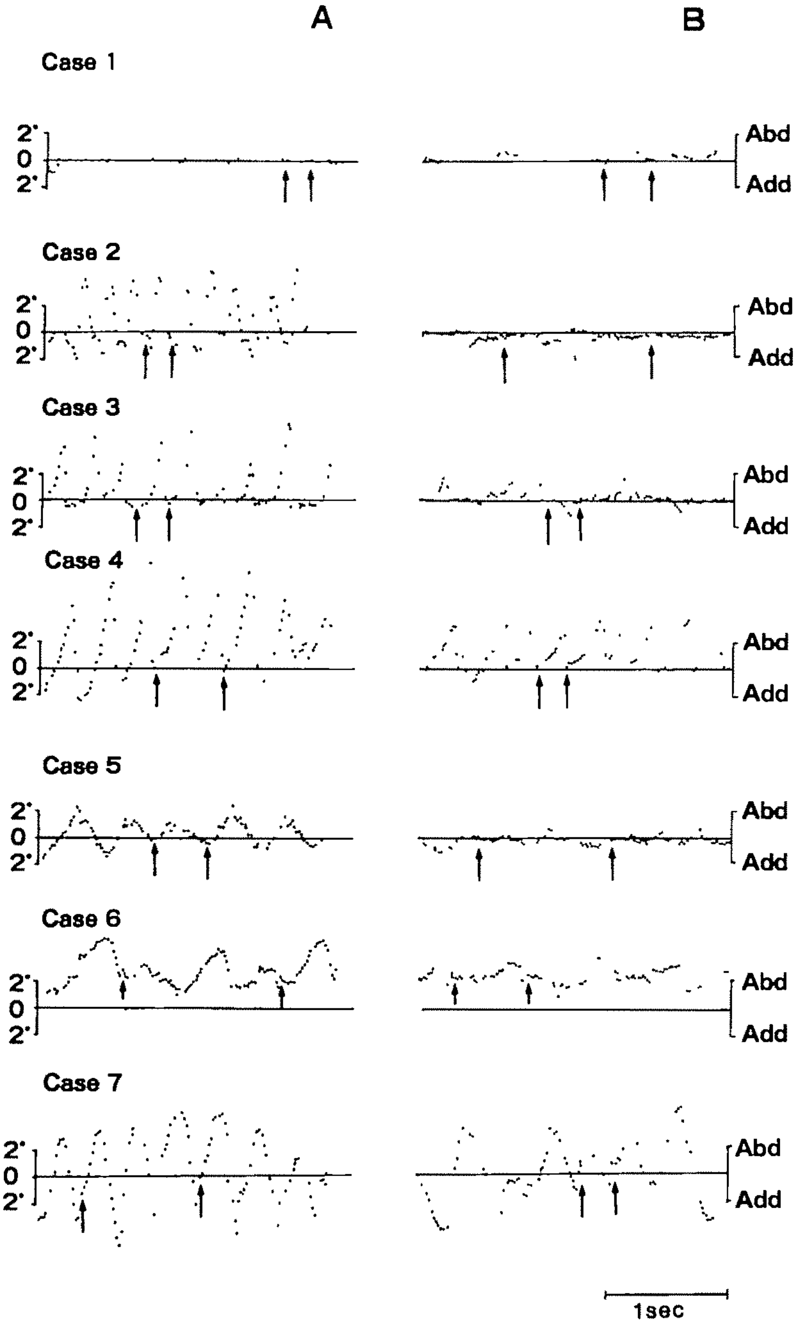


Figure 2 Waveforms for all cases prior to (A) and with (B) voluntary suppression are shown. Cases 1, 2, 3, and 4 are jerky, while case 5 is pseudopendular with foveating saccades, and cases 6 and 7 are pendular. Foveation is shown by small arrows Excellent suppression can be seen in cases 1, 2, 3, and 5.

togram maximum percentage rate improved from 53% to 86% and was again centred.

Case 4 showed a leftward jerk nystagmus. With voluntary suppression the waveform did not change shape significantly, but the amplitude of the nystagmus was greatly reduced. Foveation occurred at the end of the quick phase of the nystagmus, and a slight prolongation of foveation can be seen with voluntary suppression. The histogram maximum improved from 20% to 29%.

Case 5 had a pseudopendular nystagmus with foveating saccades. The amplitude of the nystagmus was not large. With voluntary suppression foveation increased and the amplitude decreased. The histogram maximum increased from 46% to 69%.

In case 6 we observed a pendular nystagmus with foveating saccades. Notice that the entire waveform is shifted approximately 2° to the nasal side of the foveola. With voluntary suppression the amplitude dropped, but the eccentric fixation did not change. The maximum rate in the histogram shifted from 28% to 53%.

Case 7 also had a pendular nystagmus with foveating saccades. Since the foveating saccade passed through the foveola, the foveation time was extremely short. With voluntary suppression there was a reduction in frequency but the amplitude remained unchanged. The maximum rate in the histogram changed from 19% to 20%.

CHANGE IN PARAMETERS WITH VOLUNTARY SUPPRESSION

In all cases presented here the parameters of nystagmus – namely, the amplitude, frequency, intensity, and the foveation time – improved with voluntary suppression. Average data for each parameter is shown in Table II. All cases showed a reduction in amplitude. Frequency dropped in five cases, and increased slightly in the pseudopendular (no 5) and pendular (no 6) nystagmus cases. Foveation time was prolonged in all cases. Histogram maximum values also improved in all cases. The right-hand colum summarises the waveform changes observed.

Subjects with good visual acuity (nos 1, 2, and 3) had a foveation time of over 300 ms out of each second prior to biofeedback treatment. With biofeedback-induced voluntary suppression this value improved to over 700 ms. Clearly voluntary suppression was effective in prolonging the foveation time.

Discussion

The infrared fundus television camera can cover an area of about 20° horizontally and vertically, so we have selected patients with a null point in the primary position or close to the primary position. By limiting subjects in this way one can obtain a precise picture for analysis of the nystagmus. This is the best method available for direct observation of foveation.

The jerky type of congenital nystagmus foveates at the termination of the quick phase. However, in case 2 the foveation occurred during the slow phase of nystagmus as shown by the arrows. This type of waveform, in which foveation did not exist immediately after the quick phase, was not included in Dell'Osso's classification of congenital nystagmus. Recently we observed another case which was quite similar to it. As seen from commercial electric nystagmography recordings, this should be classified as a dual jerk nystagmus. It is interesting to note that foveation is being made during the slow phase. These findings suggest that dual jerk nystagmus may require classification into two subcategories – one in which the foveation is performed by saccade and another in which foveation is made during the slow phase. An almost similar case has been recorded recently by Bedell *et al.*[11]

The nystagmus of case 3 was classified as jerk with extended foveation prior to voluntary sup-

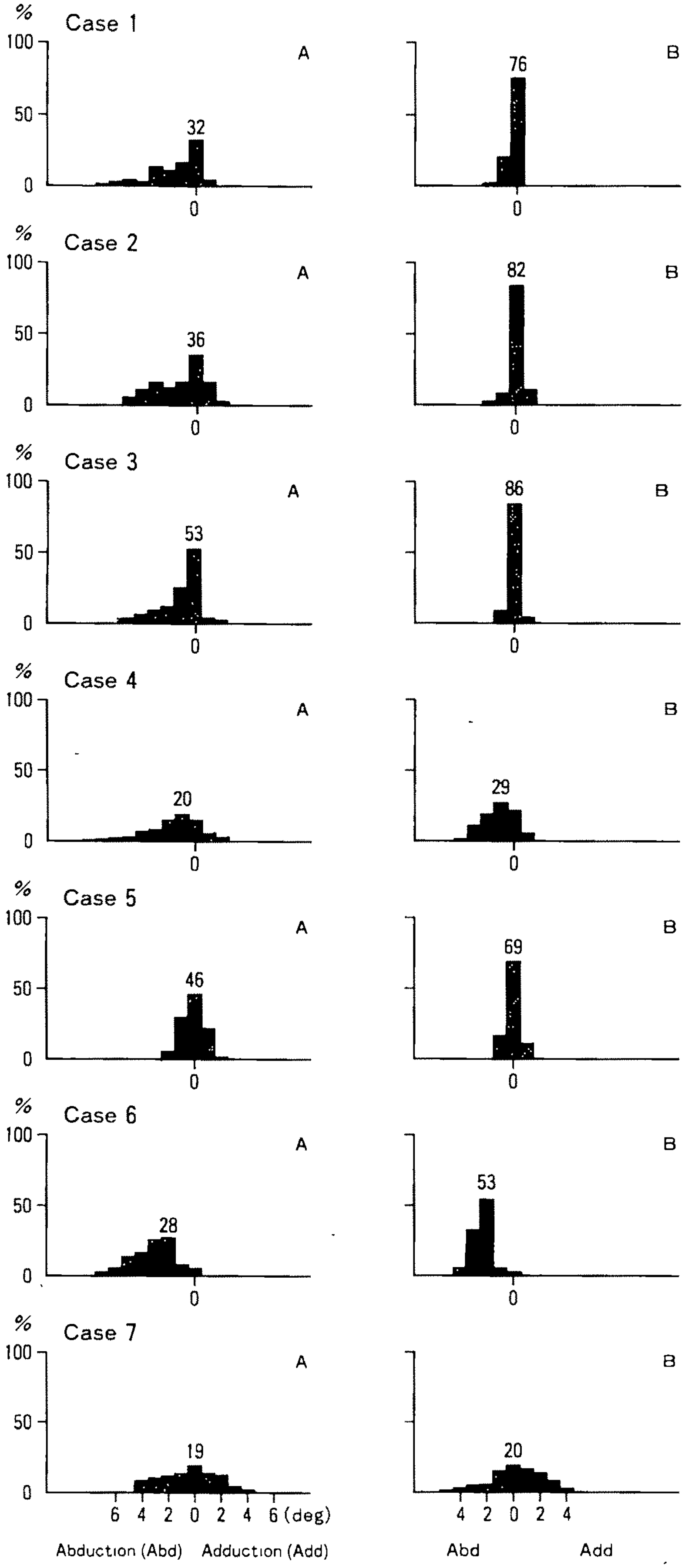


Figure 3 The position of the target in relation to the foveola. The ordinate of the histogram shows the frequency distribution as a percentage. The abscissa indicates the position of the target in relation to the foveola prior to voluntary suppression (A) and with voluntary suppression (B). Numbers above the histogram peaks indicate the maximum dot density in percentages: that means location of the eye within the central or, in cases 4 and 6, eccentric zone.

pression. With voluntary suppression the nystagmus changed to both jerk with extended foveation and frequent bias (direction) shifts and to a bidirectional jerk type. Dell'Osso[12] reported that 87% of congenital nystagmus cases had multiple waveforms in any given patient. The change of waveform is induced by changes in the angle of gaze, emotional state, visual stimulation, fixation effort, etc. We found that, in electric nystagmography recordings in case 3, the bidirectional jerk waveform was not present in any angle of gaze prior to voluntary suppression, but with voluntary suppression the bidirectional jerk appeared. This suggested that the waveform change induced by voluntary suppression may involve a different mechanism from that used when the nystagmus waveform changes with angle of gaze.

On the other hand the nystagmus waveform in cases 4 to 7 did not alter with voluntary suppression. These cases showed only a change in amplitude. Foveation in case 4 was made at the termination of the quick phase, and this remained the same with voluntary suppression, though amplitude was reduced. According to Dell'Osso's report[12] subjects with pendular nystagmus with foveating saccades usually have multiple waveforms, such as jerk with extended foveation or pseudocycloid and pendular. In cases 5 and 6 there was a reduction in amplitude with voluntary suppression, while the frequency did not reduce. A slight increase in foveation was seen, and the precision of the foveation improved, with the disappearance of the overshoot and undershoot saccades which existed prior to suppression in cases 6 and 7. These results are summarised as an extension of the foveating time, and it was best demonstrated in the histogram analysis. We have seen that prolongation of foveation with biofeedback training is more effective in jerk than in pendular nystagmus.

The exact mechanism of voluntary suppression of nystagmus by means of an auditory cue remains unclear. Increasing muscle tension in the lids as well as changes in the tonicity of the laryngeal or pharyngeal muscles may modulate the intensity of the nystagmus amplitude. Embryologically the trigeminal, facial, glossopharyngeal, vagus, and recurrent laryngeal nerves all develop from the same branchiogenic nerve. Biofeedback training possibly makes use of these common pathways, which may still exist after birth.

As to visual acuity, several studies have shown little improvement in visual acuity despite an improvement in the nystagmus.[5] We have previously reported that contrast sensitivity was improved by only 0·1–0·2 log unit over a wide range of spatial frequencies.[13] A similar result was seen with prism training,[14] in which the induced convergence triggered suppression but caused a decrease in contrast sensitivity[13] due to convergence-induced overaccommodation.

In some cases we have seen an improvement in the rate of central zone foveal fixation with no change in waveform. Furthermore, visual input plays an important part in maintaining centric fixation during foveation, so the waveform changes and reduction in the amplitude during

Table 2 Comparison of parameters prior to and with voluntary suppression (average values)

	Amplitude (deg)		*Frequency (Hz)*		*Intensity (deg×Hz)*		*Foveation time (ms)*		*Maximum histogram rate (%)*		
Case	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*Change in waveform*
1	7·2	3·1	4·4	1·2	31·7	3·7	374	767	32	76	Almost normalised
2	4·5	2·3	4·5	0·3	20·3	0·7	344	912	36	82	Normalised
3	2·8	2·0	3·8	1·8	10·7	3·6	573	864	53	86	Bias shifts and bidirectional jerk
4	5·5	3·1	3·7	3·3	20·4	10·2	200	304	20	29	Jerk (no change)
5	2·4	1·3	1·8	2·1	4·3	2·6	204	538	46	69	Pseudopendular (no change)
6	3·1	1·9	2·3	2·7	7·1	5·1	254	349	28	53	Pendular with foveating saccades (no change)
7	6·1	5·3	3·1	2·3	18·9	12·2	133	193	19	20	Pendular with foveating saccades (no change)

A: prior to voluntary suppression B with voluntary suppression.

self control may be attributed to improvement in some visual function such as visual attention or deliberate viewing.

The authors express their thanks to Dr Louis Dell'Osso for his kind help in establishing the work. This work was in part supported by the grant no 01870075(1990) from the Ministry of Education in Japan.

1 Bagolini B. Orthoptic and prismatic treatment of congenital nystagmus. In: Reinecke, ed *Strabismus* New York: Grune and Stratton, 1978. 191–201.

2 Larmande P, Pautrizel B. Traitement du nystagmus congénital par le 5-hydroxytryptopane *Nouv Presse Med* 1981; 10: 3166.

3 Yee RD, Baloh RW, Honrubia V Effect of baclofen on congenital nystagmus In: Lennerstrand G, *et al*, eds. *Functional basis of ocular motility disorders* Elmsford, NY: Pergamon, 1982: 151–7.

4 Abadi RV, Carden D, Simpson J. A new treatment for congenital nystagmus. *Br J Ophthalmol* 1980; 64: 2–6

5 Ciuffreda KJ, Goldrich SG, Neary C Use of eye movement auditory biofeedback in the control of nystagmus. *Am J Optom Physiol Opt* 1982; 59: 396–409.

6 Ishikawa S, Tanakadate A, Nabatame K, Ishii M Biofeedback treatment of congenital nystagmus. *Neuro-ophthalmology Jpn* 1985, 2: 58–64.

7 Ishikawa S, Ozawa H, Fujiyama Y. Treatment of nystagmus by acupuncture In: Ishikawa S, ed. *Highlights in neuro-ophthalmology*. Amsterdam. Aeolus, 1987: 227–32

8 Dell'Osso LF, Daroff RB. Congenital nystagmus waveform and foveation strategy *Doc Ophthalmol* 1975; 39: 155–82.

9 Yee RD, Wong EK, Baloh RW, Honrubia V A study of congenital nystagmus: waveforms. *Neurology* 1976; 26: 326–33.

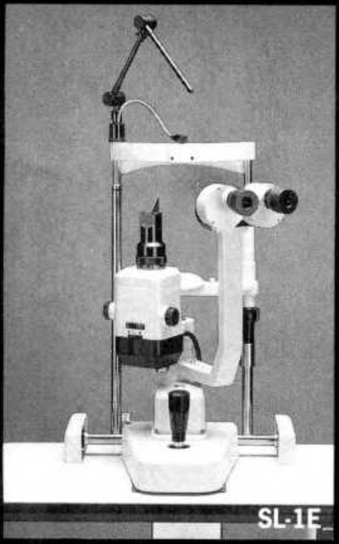
10 Tani I Study on congenital nystagmus. A new method of analysis of congenital nystagmus by infrared television fundus camera *Nippon Ganka Gakkai Zasshi* 1981; 85: 25–32

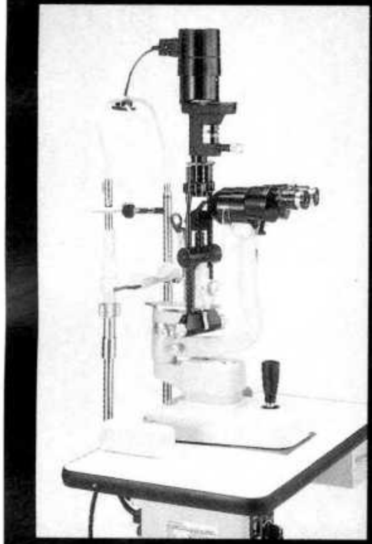
11 Bedell HE, White JM, Abplanalp PL Variability of foveations in congenital nystagmus. *Clin Vis Sci* 1989, 4: 247–52

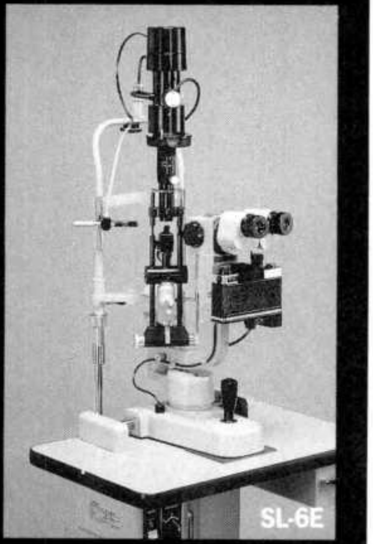
12 Dell'Osso LF. Congenital, latent and manifest latent nystagmus – similarities, differences and relation to strabismus. *Jpn J Ophthalmol* 1985; 29: 351–68.

13 Matsubara K, Ukai K, Ito M, Ishikawa S. Concurrent measurements of congenital nystagmus intensity and contrast sensitivity with respect to voluntary suppression of nystagmus *Jpn Rev Clin Ophthalmol* 1988; 82: 310–3

14 Dickinson CM. The elucidation and use of the effect of near fixation in congenital nystagmus. *Ophthalmic Physiol Opt* 1986; 6: 303–11.







SL-1E
- 14mm slit illumination
- Omni directional joystick
- Variable magnification capability
- Built-in filters
- Halogen illumination

SL-3E
- Omni directional joystick
- Two fixation targets
- Convenient, lever-controlled magnification change
- Slit beam inclination
- Four built-in filters
- Infinitely adjustable slit width and length
- Pachometer attachment

SL-2E
- Convergent binocular tubes enhance the examination
- Omni directional joystick
- Three-position magnification
- Infinitely adjustable slit width and length
- Built-in filters
- 35mm photographic attachment

SL-6E
- Convergent binocular tubes for unprecedented viewing
- Omni directional joystick
- Five-position magnification
- Four built-in filters
- 35mm photographic attachments
- Polaroid attachment model PA-8S
- Video attachment
- Non-contact specular attachment
- Pachometer attachment
- Observation tube

In keeping with our philosophy of supplying only top quality equipment, Keeler are now the exclusive distributors for TOPCON.

The full range of Topcon slit lamps allows the practitioner to choose exactly the right instrument for his particular needs.

Within the range, Topcon now offers high magnification versions of their most popular slit lamps. These are illustrated opposite, and the details listed below.

If a permanent record is required, then this is achievable with photographic attachments which allow the use of 35mm, Polaroid or, in the case of the SL-6E, video recording.

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

LONDON CENTRE
Keeler Martin and Tomkins, 38 Margaret Street,
Cavendish Square, London W1A 4NS
Telephone: 01-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
Telephone: (0236) 721214 Fax: (0236) 721231

ORMATION

ESENTATION

ar colourless solution in a plastic
per bottle. Glauline is available in
strengths containing 0.1%, 0.3%
6% w/v metipranolol together
benzalkonium chloride 0.01%
s a preservative.

ES

line is a beta adrenoceptor
king agent used in the topical
ment of chronic open-angle
coma and other conditions in
h intra-ocular pressure is elevated
e normal levels.

SAGE AND
INISTRATION

ecommended dosage is one drop
led into the affected eye(s) twice
. Newly diagnosed patients with
ar hypertension or chronic
-angle glaucoma should be treated
e first instance with Glauline
, changing to a higher strength if
uate control of intra-ocular
ure is not achieved or maintained.
nts on existing therapy, whether
t this is to be continued, should
ve Glauline 0.3%. Glauline 0.6%
ld be reserved only for patients
se intra-ocular pressure is not
uately controlled with 0.3%
line and for whom the prescribing
sician does not wish to add
tional therapy. Patients with
coma should not be treated with
Glauline as initial therapy.

NTRA-INDICATIONS,
RNINGS, ETC

use of Glauline is not
mmended in patients with
uctive airways disease, cardiac
ure or hypersensitivity to
pranolol. Beta blockers should
be given with verapamil and
er drug should be administered
n several days of discontinuing
other. As absorption into the
lation is possible, Glauline should
be used with caution in patients
dy receiving similar drugs by
h or where systemic use of beta
kers is contraindicated. In
cular, care should be taken in
nts with sinus bradycardia and
er than first degree heart block.
ough there is no evidence to
gest that metipranolol has
ogenic properties, its use during
nancy should be avoided, unless
otential benefits are considered to
eigh the possible hazards. No
cal trials in children have been
ed out. Glauline should not be
in patients fitted with soft
rophilic) contact lenses. There
been a small number of reports of
s of granulomatous anterior uveitis
ring in elderly patients using 0.6%
line. In any case where a patient
s symptoms or signs suggestive
terior uveitis, Glauline should be
drawn and an alternative ocular
tensive agent substituted.

ARMACEUTICAL
CAUTIONS

uline should not be diluted or
ensed from any container other
the original bottle. The unopened
uct has a shelf life of 3 years, but
ith other eye drops the contents of
bottle should be discarded one
th after opening.

GAL CATEGORY - POM

CKAGING QUANTITIES

uline is supplied as a sterile
halmic solution in a 5ml plastic
per bottle.

RTHER INFORMATION

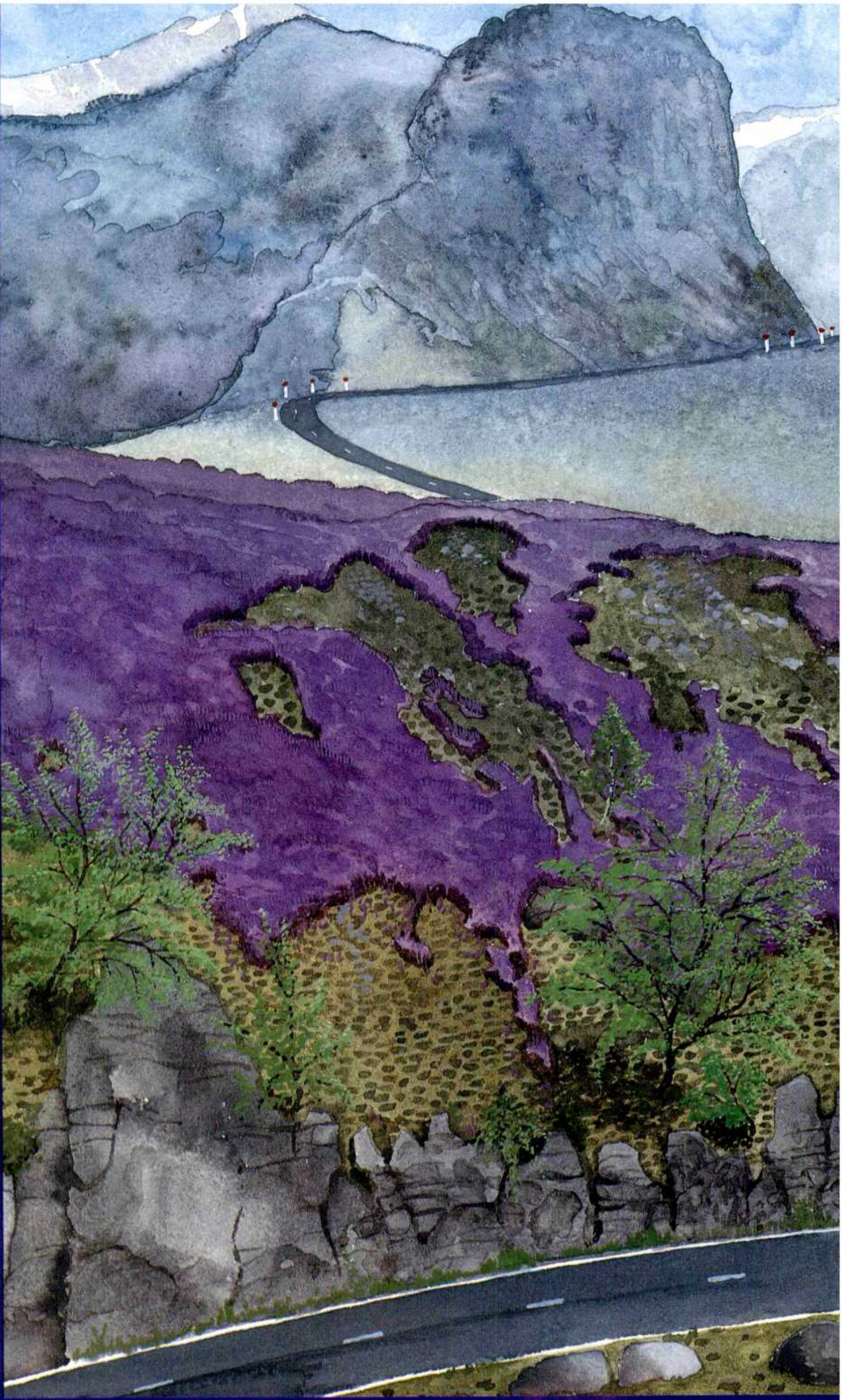
uline has little or no effect on pupil
or accommodation. Glauline is
erally well tolerated but some
ents may complain of a slight
ging which soon passes off.
sient headaches have also been
rted.

ODUCT LICENCE
MBERS

line 0.1% 0033/0104
line 0.3% 0033/0105
line 0.6% 0033/0106

SIC NHS PRICE

- 0.1% £4.03, 0.3% £4.67, 0.6%
5.



Glauline

METIPRANOLOL

*Trade Mark

Smith & Nephew Pharmaceuticals L
Bampton Road, Harold Hill
Romford, Essex, RM3 8SL, England
Telephone: 04023 49333
Telex: 898058 SMINEPG
Fax: 04023 71316
Smith + Nephew

Which is the natural tear and which is Tears Naturale™?

Tears Naturale ophthalmic solution was developed exclusively for dry eye treatment, alleviating dry spots associated with both aqueous and mucin deficiencies.

This close similarity to the action of natural tears is made possible by the unique Duasorb™ polymer system contained in Tears Naturale.

The Duasorb polymer system mimics the action of conjunctival mucin by increasing wettability of the ocular surface and stabilising the tear film.

The low viscosity and high retention time of Tears Naturale helps to ensure patient comfort, patient satisfaction and, therefore, patient compliance.

Tears Naturale: so near to tears.

Send for full details to:

TEARS NATURALE™
Dextran 70 + Hydroxypropyl Methylcellulose

Alcon
Dedicated to Excellence
Alcon Laboratories (UK) Ltd
Imperial Way Watford Herts WD2 4YR
Telephone: 0923 246133
Fax: 0923 243331

TM denotes trademark of Alcon Laboratories

Presentation: Dextran 70 0.1% and Hydroxypropyl Methylcellulose 0.3% in a sterile solution preserved with Benzalkonium Chloride BP 0.01% and Disodium Edetate BP 0.05%. **Clincal Uses:** A soothing solution for use as an artificial tear and lubricant in the relief of dry eye syndromes associated with deficient tear secretion or deficient mucous. **Dosage and Administration:** Instill 1 or 2 drops into the eye(s), as frequently as to relieve eye irritation symptoms. **Contra-indications:** The product contains Benzalkonium Chloride, and should not be used when soft contact lenses are being worn. **Precautions:** If irritation persists, discontinue use. **Product Licence No:** 0649/0031.

British Journal of Ophthalmology, 1990, 74, 477–480

A study of the causes of non-compliance by patients prescribed eyedrops

A J Winfield, D Jessiman, A Williams, L Esakowitz

Abstract

An investigation into the causes of non-compliance by patients using eyedrops has been undertaken by questionnaire, ability tests, and by tests on eyedrop bottles. The results indicate a high prevalence of non-compliance, compounded by an inability adequately to instil a drop into the eye. About half the patients had difficulty aiming the drop, and other problems including squeezing the bottle, blinking, and seeing the tip of the bottle. Ability tests included a measurement of the grip strength of patients to complement measurement of the force required to expel a drop from a bottle. Some patients, particularly those with arthritis, could not generate enough force to squeeze a bottle. These same patients also had difficulty with the other movements required to administer drops. While some attempts have been made to produce devices to assist with eyedrops which can improve the aim of the patient, none give assistance in expelling a drop. An additional problem found was the reluctance of patients to admit to medical staff that they experienced any difficulty with their drops.

It is well established that complience of patients with a prescribed treatment is often inadequate. This may be due to a complex interaction of factors, prime among them being lack of knowledge, inability, or disinterest. Eye preparations are no exception.[1] Several teams have undertaken studies in an attempt both to enumerate the extent of the problem and to understand its origin.

One approach has been to use a special drop bottle with an electronic device to record drop administration. In one study[2] such a device showed that 41% of patients missed six or more doses over a 30-day period. A similar study[3] found that over half the patients missed 20% of their prescribed doses. Other studies have relied on interview[4,5] and observation[6,7] and have produced similar results. All these studies were undertaken with patients regularly using eyedrops for glaucoma, one of them[6] indicating that 13% of patients observed were unable to place drops in both eyes after several attempts.

Interviewing patients using eyedrops after cataract surgery[8,9] revealed a similar range of problems and non-compliance. Other workers have also demonstrated problems with drop size, reporting a wide variation in drop size from commercial eye drops[10] and variation in the number of drops actually expelled by patients.[7]

Collectively these studies have shown that many patients have experienced difficulties in self-administration of eyedrops. Some possible reasons for this have been elucidated and some 'at risk' groups identified.[11] Many of the problems appear to be physical, that is, related to the ability of the patient to aim a drop accurately into the conjunctival sac. To help them several devices have been used and reported on. Letocha[12] reviewed those available in 1985, which all attempted to help the patient aim more effectively. One was a plastic support device,[13] another consisted of modified sunglasses,[14] while another had a system of mirrors to help the patient see the dropper tip.[15] Later published ideas have included a modified glasses frame[16] and a cone shaped device to support and direct the dropper.[17] The reports do not indicate whether the devices were successful in achieving their objective. However, it appears that their design was based on perception of a problem rather than on detailed analysis of factors involved. In addition one manufacturer has modified the bottle to assist in expelling a drop (MSD Ocumeter).

A review[18] has reported that there are several problems which patients experience and which lead to non-compliance and concluded that it is therefore unlikely that one answer will be found. Because of the relative lack of published evidence it was decided to undertake a study aimed at elucidating the physical problems experienced by patients during eyedrop administration and from the results to derive guidance on the features required by a compliance aid.

Material and methods

Information was obtained by questioning patients, by ability tests, and by a physical evaluation of eyedrop bottles.

QUESTIONNAIRE

For the questioning the interviewer deliberately created an informal, relaxed atmosphere before asking a series of open-ended questions. Where possible, discussion was allowed to develop. In this way 200 patients attending the Eye Outpatients Department at Aberdeen Royal Infirmary were interviewed irrespective of their condition, only provided they were using eyedrops. The questions used explored the patients' knowledge of their condition and its treatment, whether their compliance was good or bad and the reasons for this, how they administered their drops, any problems encountered, and whether they would welcome a compliance aid if a suitable one was available.

ABILITY TESTS

Thirty patients in the eye surgery ward at

Pharmacy and Medicines Research Unit, School of Pharmacy, Robert Gordon's Institute of Technology, Aberdeen AB9 1FR
A J Winfield
D Jessiman

Aberdeen Royal Infirmary, Aberdeen, Pharmacy Department
A Williams

Ophthalmology Outpatients Department
L Esakowitz

Correspondence to
Dr A J Winfield, School of Pharmacy, Robert Gordon's Institute of Technology, Schoolhill, Aberdeen
AB9 1FR.

Accepted for publication
1 March 1990

Woodend Hospital, Aberdeen, agreed to undergo a series of ability tests. 10 ml bottles of hypromellose eyedrops *BNF* were used.

(1) Patients were asked to expel one drop into a preweighed vial. The increase in weight was recorded.

(2) A sheet with a series of concentric circles was used as a target. With the wrist resting on a block at a height of 4 cm the patients were asked to place a drop on the centre of the target.

(3) The patients were asked to instil a drop of hypromellose into one eye of their choice unaided. They were asked to repeat the process using the Easidrop.

(4) A dynamometer (Vigorimeter) was used to measure the pressure of squeeze exerted by finger and thumb (as on a bottle) and by the full hand.

EVALUATION OF BOTTLE

A test rig was used to measure the force required to expel drops of hypromellose from 5, 10, and 20 ml bottles (Cascelloid Division, BXL Containers Ltd). The force was applied at the midpoint on the bottle side, away from the seam. Further tests, on 10 ml bottles only, were carried out to find the effects of the bottle seam, the position of applying the force on the bottle side, the quantity of liquid in the bottle, and the storage temperature on the force required to expel a drop.

Results and discussion

QUESTIONNAIRE

The patients (average age 62, range 9–92) were being treated for glaucoma (32%), following surgery (25%), dry eye (10%), irritation and injury (10%), conjunctivitis, ulcers, and other conditions. Most knew the nature of their condition (96%) and were satisfied with their understanding of it.

Compliance patterns are shown in Table I. Any assessment of a compliance level is unreliable. By using a relaxed approach it was hoped that patients would be more open than in a more formal situation. Their readiness to admit problems and shortcomings would indicate a good level of accuracy and reliability in their responses. This being the case, 75% of patients complied well with instructions. Those who did not admitted a poor motivation owing to not understanding the function of the drops or an inability to use them. This finding suggests that if patients are well informed, as they were in this sample, their motivation is not a major problem in achieving compliance.

Table 1 Patterns of compliance in administration of eyedrops

Compliance	*Number of patients*
Used drops as directed	128 (64%)
Missed an occasional dose	24 (12%)
Missed up to two doses per week	32 (16%)
Other responses	16 (8%)
Administered own drops	124 (62%)
Did so if no one else available	34 (17%)
Always obtained assistance	42 (21%)
Had never tried self administration	16 (8%)

Table 2 Problems encountered by patients during self medication with eyedrops

Problem	*% Patients*
Directing the bottle (miss frequently)	36
Directing the bottle (miss occasionally)	13
Shaky hand	8
Squeezing the bottle	20
Blinking	12
Poor visibility of tip of dropper	13
Prodding eye with tip of dropper	9
Reading labels and identifying bottle	14

Over a third of patients did not administer their own drops regularly, with 21% always using assistance. Within this latter group, 8% had never tried self administration, 4% found it took too long, while the remaining 9% had tried but lacked the ability to place the drop in their eye. In total, 57% of patients admitted having some difficulty administering their drops. The main problems are presented in Table II. Discussion with patients indicated that lack of confidence was a major factor, particularly fear of prodding the eye. As a result the bottle was often held too far from the eye, making the aim more difficult and encouraging the blink reflex. Older patients experienced physical problems in raising the arm, tilting the head, and in holding and squeezing the bottle. Some patients found breaking the tamper-proof seal on a new bottle difficult.

The possibility of a compliance aid was welcomed by 78% of patients, but none were aware that any aids were available. Surprisingly, 72% said that the interview was the first time that they had been asked whether they had problems, while 69% said that they would not tell a doctor of their problems even if asked. This reluctance on behalf of patients was reflected in the lack of awareness among medical staff of the problems experienced by the patients.

ABILITY TESTS

(1) The weight of eyedrop solution in each vial varied from 0·03 g to 0·07 g (mean 0·39 g). Several patients expelled more than one drop.

(2) Most patients said they thought they had aimed the target well. The results are presented in Table III.

(3) Only six patients (20%) instilled a drop unaided first time. This was increased to 26 (87%) with the Easidrop device. This latter figure may be artificially high because all the patients were laid flat or almost flat so that no head-tilting was necessary.

(4) The patients had a wide range of grip strength. The pressure recorded was converted to a force based on the area of the Vigorimeter

Table 3 Accuracy of aim of patients as measured by means of target 4 cm below wrist height

Distance from centre of target	*Number of patients*
Within 1·5 cm (simulating eye)	9
Between 1·5 cm and 3 cm	14
Greater than 3 cm	7

bulb. The finger and thumb forces varied from 8·35–100·2 N, while full grip values were between 15·03 and 183·7 N. Thus the force is roughly doubled by using a full grip.

EVALUATION OF BOTTLES

Data for the average force required to expel a drop are presented in Table IV. A wide spread of results was obtained from the bottles tested, not just between bottles but also depending on the number of previous squeezes or whether it had been held in the hand for a few minutes. So at best these results can give only an indication of the forces required to expel a drop in various situations. Storage in a fridge, or pressing on the seam, increased slightly the force required. However, there was a marked increase as a bottle was progressively emptied, presumably because of the higher compressibility of air than the hypromellose solution.

The real significance of the results becomes obvious when these forces are compared with the force which the patients were able to exert. For most there was no problem, but some (approximately 13% of our sample) could not expel a drop from the bottle. (The questionnaire sample gave a higher figure of 20%.) In general these patients are those who have arthritic conditions, which also reduces their ability to raise the dropper to their eye. It may be physically impossible for this group to self-administer their drops without some additional aid.

For patients who were marginal in their ability to expel drops a second problem emerged from both the questionnaire and the ability tests. As the force being applied approached the limit of their capability, so the wobble of the hand increased. The questionnaire suggested that a further 8% were affected in this way, while observation of the practical tests suggested a much higher figure (approaching 50%). From these data it appears that 25%–50% of patients using eyedrops may have severe physical difficulty in administering them. This will manifest itself in failure to apply them, administering more than one drop (also reported by Kass,[7]), or opting out and either not trying or using a second person (30% of patients). A shaking hand affected the ability of some patients to aim accurately. The ability tests (Table III) showed that only 30% of patients could place a drop within 1·5 cm of the centre of a target (that figure taken to be the approximate size of the eye), and 47% were within 3 cm. This test was carried out in front of the patients, who could clearly see what they were doing. Corroborative evidence came from the questionnaire, where 49% admitted to missing the eye at least occasionally, and from the observation of patients placing drops in the eye, where only 20% managed it first time.

From this work it appears that we have identified two interrelated problems with the self administration of eyedrops: firstly, the lack of physical acuity, and secondly the inability to aim adequately. At present there is in the UK only one aid to assist with administering eyedrops – the Easidrop (produced by Quoteforce, UK). This screws on to the standard bottle neck until the dropper tip is level with a guide mark and, being shaped like an eyebath with cut-away sides, directs the tip of the bottle towards, but clear of, the eye. It will, therefore, improve the aim of patients – as was found in the ability tests – though it does not adequately account for gravity in a non-supine patient. Thus patients have to tilt their head back a long way, which may be difficult for those who are elderly or arthritic. It also reduces the related problem of prodding the eye and lack of visibility of the tip, but does not help in expelling a drop. Several devices aimed at improving application have been described,[12-17] but they are all concerned only with improving the aim.

Table 4 Average force required to expel a drop from an eyedrop bottle at the midpoint on the side away from the seam at room temperature (unless stated to the contrary)

Bottle/condition	*Average force required (N)*
5 ml	13·24
10 ml	11·76
20 ml	8·82
10 ml stored in fridge	13·22
10 ml midline on seam	12·84
10 ml half empty	17·64

Apart from the evidence we have produced, demographic trends indicate that the number of patients experiencing difficulty will increase rather than decrease. Difficulty in administering drops increases with age. Projections indicate that the population of 85 years old and above will increase by a third over the next 10 years. Unless many of the patients are able to self-administer eyedrops, very heavy demands will be placed on health service resources. Twelve years ago it was estimated that there were 100 000 cases of chronic open-angle glaucoma.[4] This figure will have increased, and it takes no account of other conditions requiring the use of eyedrops. Because of this we have taken steps to develop an aid which will assist with the problems identified – namely, aim, tilting the head, squeezing the bottle, seeing the drop approaching the eye. It will also help in breaking the tamper-proof seal. A prototype device (Fig 1) is currently undergoing evaluation with patients in both community and hospital. If any compliance aid is to be beneficial, the patient must be aware of its existence. In our questionnaire we found a very disturbing reluctance on the part of patients to

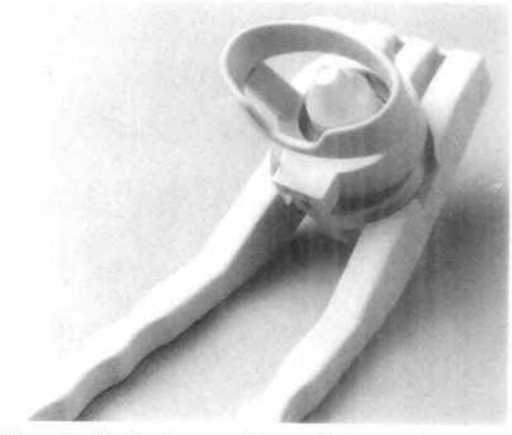


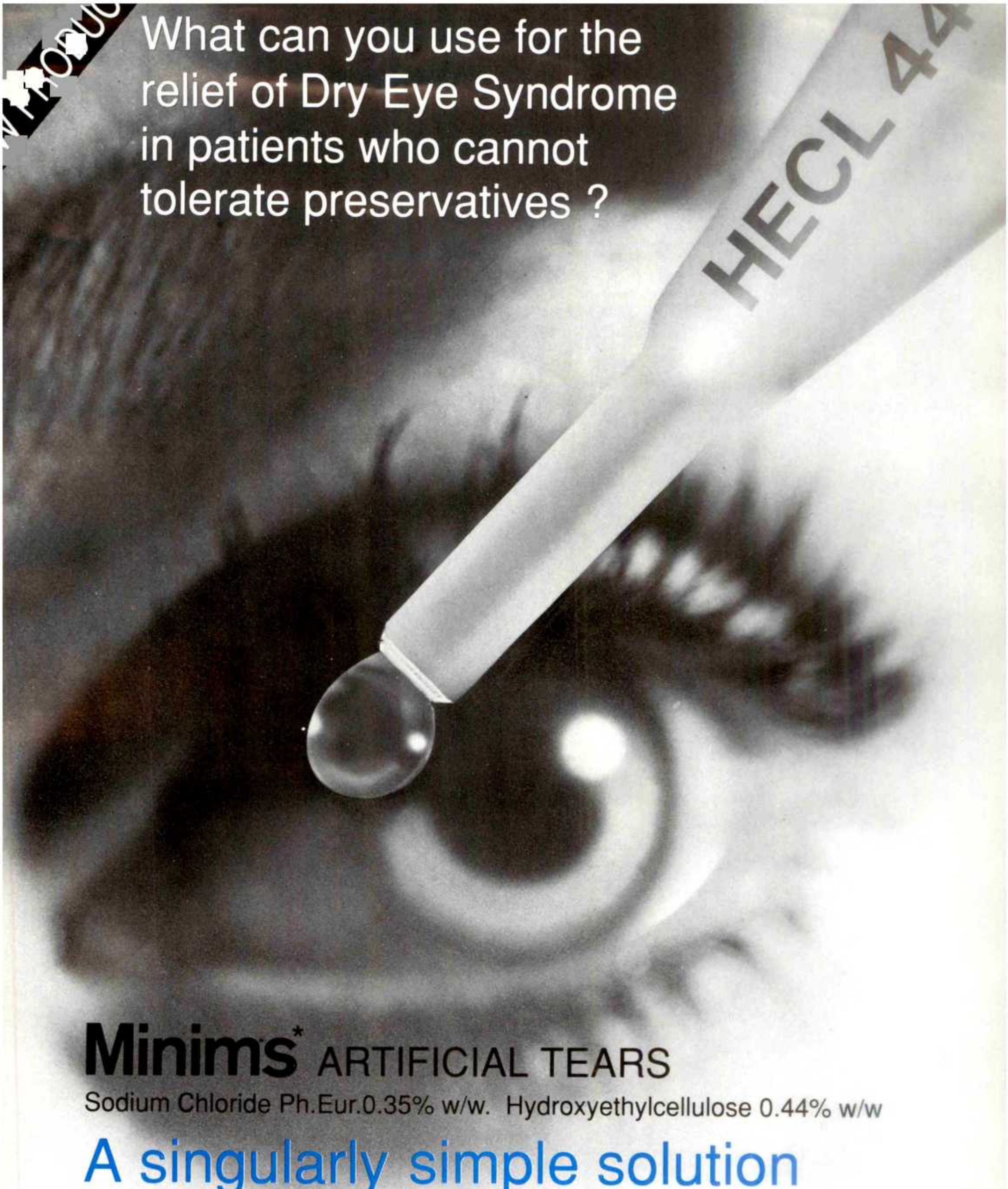
Figure 1 The Opticare compliance aid, developed as a result of this study in an attempt to ease the problems experienced in the self administration of eyedrops. The device is currently undergoing evaluation with patients.

tell the doctor about any problems they had. Probably as a consequence of this we also found medical staff were less aware of their patients' problems than is desirable. No doubt the barrier to free communication can be broken down if doctors take a lead. There is probably also a need for an 'awareness campaign' aimed at patients, so that they do not feel guilty or inadequate because they have problems administering their eye-drops. The availability of a suitable device will also help patients achieve safe administration and improve compliance.

We gratefully acknowledge the assistance of Mr Ernest P Prebble in the design and production of the Opticare device and all medical and nursing staff and patients at the eye clinic and eye wards in Aberdeen hospitals.

The authors have no financial interest in the devices mentioned in this paper

1 Van Buskirk EM The compliance factor *Am J Ophthalmol* 1986; **101**: 609–10
2 Norell SE, Granstrom P-A. Self-medication with pilocarpine among outpatients in a glaucoma clinic. *Br J Ophthalmol* 1980; **64**: 137–41.
3 Kass MA, Meltzer DW, Gordon M, Cooper D, Goldberg J Compliance with topical pilocarpine treatment *Am J Ophthalmol* 1986; **101**: 515–23
4 MacKean JM, Elkington AR Compliance with treatment of patients with chronic open-angle glaucoma. *Br J Ophthalmol* 1983, **67**: 46–9.
5 Kass MA, Hodapp E, Gordon M, Kolker AE, Goldberg I Patient administration of eyedrops interview. *Ann Ophthalmol* 1982; **14**: 775–9.
6 Brown MM, Brown GC, Spaeth GL. Improper topical self-administration of ocular medication among patients with glaucoma *Can J Ophthalmol* 1984; **19**: 2–5.
7 Kass MA, Hodapp E, Gordon M, Kolker AE, Goldberg I Patient administration of eyedrops: observation, Part II *Ann Ophthalmol* 1982; **14**. 889–93
8 Smith SJ, Drance SM. Difficulties patients have at home after cataract surgery *Can J Ophthalmol* 1984, **19**: 6–9
9 Donnelly D Instilling eyedrops· difficulties experienced by patients following cataract surgery *J Adv Nurs* 1987; **12**: 235–43.
10 Lederer CM, Harold RE. Drop size of commercial glaucoma medications *Am J Ophthalmol* 1986, **101**: 691–4
11 Bloch S, Rosenthal AR, Friedman L, Caldarolla P. Patient compliance in glaucoma *Br J Ophthalmol* 1977; **61**: 531–4
12 Letocha CE. Methods for self-administration of eyedrops. *Ann Ophthalmol* 1985; **17**: 768–9.
13 Mings DE Drop aid *Ophthalmology* 1967, **71**: 368
14 Freeman MI. A method for delivery of ocular medication *Mason Clin Bull* 1975; **29**: 114–5
15 Anonymous New dispensing aid for instilling eyedrops, ointment available *Ophthalmol Times* 1985; **10**: 35
16 Law S. Development and utilisation of the eyedropper adaptation device An example of interdisciplinary cooperation *Home Healthcare Nurse* 1987; **5**: 50–1
17 Sheldon GM. Self-administration of eyedrops. *Ophthalmic Surg* 1987; **18**: 393-4.
18 Zimmerman TJ, Zalta AH Facilitating patient compliance in glaucoma therapy. *Surv Ophthalmol* 1983; **28**: 252–7



What can you use for the relief of Dry Eye Syndrome in patients who cannot tolerate preservatives ?

Minims* ARTIFICIAL TEARS

Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

A singularly simple solution

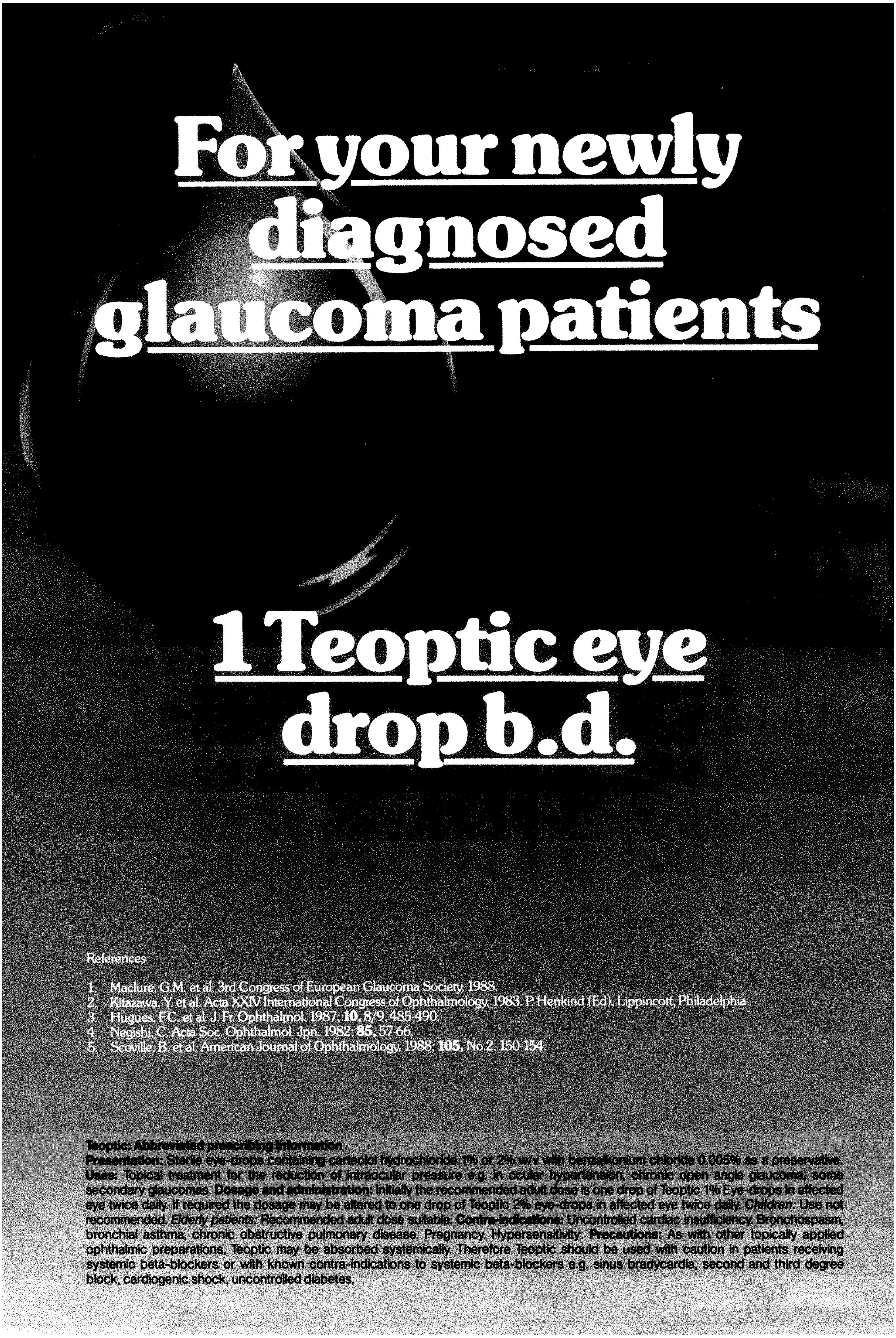
PRESCRIBING INFORMATION

● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml. Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

* Trade Mark

Smith+Nephew



For your newly diagnosed glaucoma patients

1 Teoptic eye drop b.d.

References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

Teoptic: Abbreviated prescribing information
Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity: **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

- Effectively lowers IOP[1]
- Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol *[2,3]
- Has a prolonged therapeutic effect[4] thus offering flexible b.d. dosage regimen
- Well tolerated with few local side-effects[5]
- Low concentration of benzalkonium chloride in a buffered solution.

* Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.

Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.
Teoptic is under licence from Otsuka, Japan. Further information is available on request to the above address.

AJO

AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 00029394 June 1990 Series 3, Vol. 109, No. 6

TABLE OF CONTENTS

ORIGINAL ARTICLES

Variable genotype of Leber's hereditary optic neuropathy patients Marie T. Lott, Alexander S. Voljavec, and Douglas C. Wallace

Septo-optic dysplasia in two siblings Jeffrey D. Benner, Mark W. Preslan, Edward Gratz, John Joslyn, Marcia Schwartz, and Shalom Kelman

Observations concerning patients with suspected impending macular holes J. Donald M. Gass and Brian C. Joondeph

Comparison of xenon arc and argon laser photocoagulation in the treatment of choroidal melanomas Jerry A. Shields, Lou C. Glazer, William F. Mieler, Carol L. Shields, and Mark S. Gottlieb

Bilateral choroidal osteoma in three siblings Kenneth G. Noble

Risk factors for postvitrectomy fibrin formation Glenn J. Jaffe, Daniel Schwartz, Dennis P. Han, Mark Gottlieb, Arthur Hartz, Daniel McCarty, William F. Mieler, and Gary W. Abrams

Spontaneous involution of subfoveal neovascularization Peter A Campochiaro, Kirk M. Morgan, Brian P. Conway, and John Stathos

Patterns of rod and cone dysfunction in Bardet-Biedl syndrome Samuel G. Jacobson, François-Xavier Borruat, and Peter P. Apáthy

Indications for and outcomes of repeat penetrating keratoplasty Christopher J. Rapuano, Elisabeth J Cohen, Steven E. Brady, Juan J. Arentsen, and Peter R Laibson

HMB-45 antibody reactivity in pigmented lesions of the conjunctiva Ben J. Glasgow, Laurie C. McCall, and Robert Y. Foos

Collagen shield delivery of amphotericin B Steven D. Schwartz, Steven A. Harrison, Robert E. Engstrom, Jr., Roger E. Bawdon, David A. Lee, and Bartly J. Mondino

Peribulbar anesthesia for strabismus surgery Reginald J. Sanders, Leonard B. Nelson, and James A. Deutsch

Limbal-based vs fornix-based conjunctival flaps in combined extracapsular cataract surgery and glaucoma filtering procedure J. Franklin Murchison, Jr., and M. Bruce Shields

Evaluation of the Tono-Pen and the Pulsair tonometers Thomas A. Armstrong

Primate trabeculectomies with 5-fluorouracil collagen implants Ben Hasty, Dale K. Heuer, and Don S. Minckler

PERSPECTIVES

Mitochondria and Leber's hereditary optic neuropathy Nancy J. Newman and Douglas C. Wallace

LETTERS TO THE JOURNAL
CORRESPONDENCE
BOOK REVIEWS
ABSTRACTS
NEWS ITEMS

The AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. © 1990, Ophthalmic Publishing Company. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

MICHAEL J. LUND
Subscription Correspondent

LINDA G. CLAUSEN
Records Manager

LAUREEN A. KOTT
Assistant to the Editor

LYNN ANN LINDVIG
Sales and Production

PATRICIA L. BERECK
Manuscript Editor

KAREN D. JOHNSON
Editorial Assistant

RENEE L. KASTAR
Assistant Media Planner

OPHTHALMIC PUBLISHING COMPANY

Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611, U.S.A.

British Journal of Ophthalmology, 1990, 74, 481–483

Extraocular muscle surgery for Graves' ophthalmopathy: does prior treatment influence surgical outcome?

Maarten Ph Mourits, Leo Koorneef, Ada M van Mourik-Noordenbos,
Helma M van der Meulen-Schot, Mark F Prummel, Wilmar M Wiersinga, Arie Berghout

University of Amsterdam, The Netherlands Orbital Centre
M Ph Mourits
L Koornneef
A M v Mourik-Noordenbos
H M v d Meulen-Schot

Department of Endocrinology
M F Prummel
W M Wiersinga
A Berghout

Correspondence to
M Ph Mourits, Orbita Centrum, Academisch Medisch Centrum A-2 116, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

Accepted for publication
8 March 1990

Abstract

We analysed the results of extraocular muscle surgery in 38 patients with stable Graves' ophthalmopathy. Fixed sutures were used in all patients. A useful field of binocular single vision was achieved in 27 patients (71%) after one operation and in seven patients (18%) after more than one, whereas double vision was persistent in four (11%). No recurrence of diplopia was seen during one year of follow-up. No differences were found in duration of eye disease, angle of deviation, or in prior forms of treatment between patients who responded well to a single operation and those who needed more surgical procedures or those who responded less well. We conclude that, although the individual outcome cannot be predicted, every patient with diplopia and stable Graves' ophthalmopathy has an 89% chance of binocular single vision after extraocular muscle surgery. Prior treatment does not appear to influence this outcome.

Ocular motility imbalance resulting in diplopia or torticollis is frequently found in patients with Graves' ophthalmopathy.[1,2] During the period of active inflammation treatment of the disease with steroids or radiotherapy is rational.[3,4] After the inflammation has subsided and the disease has stabilised the remaining diplopia can be dealt with surgically.[5] However, extraocular muscle surgery in patients with Graves' ophthalmopathy fails in at least 10% of cases.[2,6]

The aim of this study was to determine whether duration of eye disease, angle of deviation, or prior treatment (prednisone, cyclosporin, and especially orbital irradiation or orbital decompression) would influence the outcome of surgery.

PATIENTS AND METHODS

From January 1987 to December 1988 we performed extraocular muscle surgery for diplopia on 38 patients with Graves' ophthalmopathy. Ten were male and 28 female. Their age at operation ranged from 29 to 84, average 54·5 years. The diagnosis of Graves' ophthalmopathy was based on clinical findings and enlargement of the extraocular muscles on CT scan. All patients were classified in NOSPECS class 4, grade b.[7] Prior to extraocular surgery only four patients had never had any treatment for their Graves' ophthalmopathy. Nine patients had been treated with immunosuppressive treatment (including prednisone, maximum dose 60 mg/day, and/or cyclosporin, 7·5 mg/kg/day); 12 patients with orbital irradiation, total dose 20 Gy (with or without medical treatment), and 13 patients had undergone orbital decompression (after or without medical and/or radiation treatment). Eleven of the 13 patients who underwent decompression already had diplopia before this operation. All patients were euthyroid at the time of surgery and had stable eye disease, defined as: unchanging proptosis, constant angle of deviation, and stable visual acuity for at least three months. All patients experienced diplopia, which could not be relieved by prisms. Eighteen patients (47%) had hypotropia, 8 (21%) had esotropia, and 12 (32%) had both hypo- and esotropia. The range of esotropia was 8 to 45 dioptres and the range of hypotropia 4 to 22 dioptres.

A synopsis of the muscles operated on is given in Table I. In most cases a recession of the inferior or medial rectus muscle was performed. Fixed sutures were used in all patients. The amount of surgery was decided upon by the angle of deviation. For hypotropia the amount of inferior rectus recession varied from 2·5 to 5·0 mm, average 3·3 mm. Special care was taken to dissect the muscle free of all its attachments to the conjunctiva, the lower lid retractors, and the inferior oblique muscle. In one patient a complete tenotomy of the inferior and medial rectus muscle was performed. For esotropia the amount of medial rectus recession varied from 3·5 to 8·0 mm on both sides. Two surgeons (LK and MPhM) performed the operations.

The outcome of surgery was assessed three months after the operation. The field of binocular single vision was measured with the Maddox cross.[8] If no binocular single vision in primary and reading position could be acquired (if need be with prisms up to 5 dioptres for each eye), further surgery was performed.

All patients with re-established binocular single vision were followed up at least one year postoperatively for recurrences.

'Optimal response' to surgery was defined as single vision in primary and reading positions after one operation without the support of prisms. 'Suboptimal responders' were those who needed prisms up to 5 dioptres or needed more than one

Table I Synopsis of the muscles operated on in 38 patients with stable Graves' ophthalmopathy

Recession: inferior rectus	35
Recession medial rectus	39
Recession contralateral superior rectus	3
Recession inferior oblique	2
Resection lateral rectus	3
Tenotomy: inferior + medial rectus	1

Table 2 Results of extraocular eye muscle surgery in 38 patients with unchanging diplopia due to Graves' ophthalmopathy

	n	*Optimal response*	*Suboptimal response*	*Failure**
Hypotropia	18	9	7	2
Esotropia	8	7	0	1
Hypo- plus esotropia	12	5	6	1
Total	38	21	13	4
Percentage	100	55	34	11

*For definitions see text.

operation for single vision. 'Failures' were those in whom no single vision could be obtained or stronger prisms than 5 dioptres were required.

Results

Thirty-four (89%) patients achieved binocular single vision in primary and reading positions (Table II). Twenty-seven patients needed one procedure, five needed two procedures, one patient three, and one four.

None of the patients became overcorrected in the primary position, but two out of 18 patients with preoperative hypotropia showed a limitation of depression postoperatively, requiring prisms in the reading position. One patient achieved single vision in both primary and reading position with a slight head tilt. Three other patients with hypotropia were undercorrected and needed weak prisms (up to 5 dioptres) for the residual angle.

In the group of patients with esotropia all but one regained single vision after one operation without the need for prisms. In the group of 12 patients with both hypo- and esotropia six fused after one operation and five after more than one. Four eventually needed weak prisms.

Comparing optimal responders and suboptimal responders plus failures, we found no differences in sex, age, duration of eye disease, angle of deviation, or prior forms of treatment between either group (Table III).

The results of surgery were not always obvious shortly after the operation. Some patients were still hypo- or esotropic during the first month after surgery, but became orthophoric within three months. On the other hand some patients were orthophoric shortly after surgery but developed a limitation of depression after one or two months. 74% of the patients stabilised within one month and the remaining 26% within three months. Long term follow-up showed no major alterations of the field of binocular single vision in any patient.

Table 3 Comparison between optimal responders and suboptimal responders plus failures

	Optimal responders n=21	*Suboptimal responders plus failures n=17*
Male/female	6/15	5/12
General/local anaesthesia	13/8	9/8
Age (years)	52 6 (10·4)	56·7 (12·3)*
Surgeon 1/surgeon 2	6/15	6/11
Duration GO median (range)	28 (11–76 mo)	20·5 (8–48 mo)†
Prior treatment.		
no pretreatment	3	1
medical treatment only	4	5‡
radiotherapy	7	5‡
orbital decompression	7	6‡
Angle of deviation (dioptres) (given for hypotropia only)	21 (9·6)	23 (9 4)*

Notes· GO=Graves' ophthalmopathy mo=Months
Data are expressed as the mean (with standard deviation) and were analysed by the two-sample, two-sided *t* test*, the median plus range and analysed using the Mann-Whitney U test†; real numbers and analysed by the χ^2-test, corrected for small numbers ‡ None of these differences appeared to be significant

Discussion

Evans and Kennerdell reported a success in 88% of patients with Graves' ophthalmopathy after multiple procedures for diplopia,[2] Dyer in 82% after one operation.[6] Fells and McCarry, comparing fixed and adjustable sutures in patients with Graves' induced diplopia, obtained a long term success in 66% of patients operated on with fixed sutures and in 76% of patients with adjustable sutures.[9] We prefer non-adjustable rather than adjustable sutures because the technique is simpler and only one intervention is necessary. Using fixed sutures, we obtained successful results in 71% after one and in 89% after more than one procedure.

Thus at least 11% of patients with Graves' ophthalmopathy do not respond well to surgery. As stated by Char,[10] squint surgery in Graves' ophthalmopathy is not comparable to squint surgery in general. The extraocular muscles of patients with Graves' disease are taut and often bleed excessively.[6] Eyelid swelling prevents easy access to the operative field. Because of the nature of the disease, postoperative scarring is considerable. These factors explain why binocular single vision without the use of prisms is not always obtained after one or even more surgical procedures.

We hypothesised that the preoperative duration of eye disease, the angle of deviation, or the prior treatment could influence these factors. Large angles of deviation demand more extensive surgery, and this in turn might influence the surgical outcome. Furthermore it has been thought that orbital irradiation produces more extensive fibrosis, which is a well known side effect of megavoltage radiation therapy,[11] thus hampering extraocular muscle surgery. We could not detect any difference, however, in the above mentioned characteristics between the groups of optimal responders and the group of suboptimal responders plus failures. When patients pretreated with orbital irradiation were compared with those who were pretreated medically only, no difference was found between the two groups in surgical outcome. Nor was any significant difference found in relation to other types of prior treatment, duration of eye disease, or angle of deviation. These findings suggest that these characteristics have no predictive value for the outcome of surgery.

A possible cause of failure after extraocular muscle surgery for Graves' ophthalmopathy could be a relapse of the active inflammatory process. This seems highly unlikely in our patients, because features indicating activity of the disease, like changes of eyelid swelling, proptosis, and visual acuity, were absent.[5] Failures in our series may be explained by the fact that we mainly recessed the extraocular muscles, and recessions displace the centre of rotation of the eyeball, thus influencing the surgical result. This might be prevented by doing a recession together with a resection of the antagonist, as advised by Crone.[8] In this series we performed an additional resection of the lateral rectus in three patients with very tight muscles, resulting in an optimal response in two of them.

In one patient the angle of deviation did not change after the involved muscle had been completely detached from the globe. Even by pulling the eyeball into the primary position the deviation could not be changed. This can only be explained by extensive fibrosis of the orbital connective tissue system.[12] Recurrences of diplopia were not found during a follow-up period of one year, most certainly because most patients were constantly euthyroid prior to surgery, and no patient was operated on before all signs of disease activity[5] had disappeared completely.

In conclusion, this study shows that long term satisfactory results of extraocular muscle surgery in patients with stable Graves' ophthalmopathy can be achieved in almost 90% of the cases without the need for adjustable sutures. The outcome of surgery is not influenced by the duration of the disease, the preoperative angle of deviation, sex or age, or by the sort of preoperative treatment.

1 Wiersinga WM, Smit T, van der Gaag R, Mounts M, Koornneef L. Clinical presentation of Graves' ophthalmopathy. *Ophthalmic Res* 1989; 21: 73–82
2 Evans D, Kennerdell JS. Extraocular muscle surgery for dysthyroid myopathy. *Am J Ophthalmol* 1983; 95: 767–71
3 Wiersinga WM, Smit T, Schuster-Uittenhoeve ALJ, van der Gaag R, Koornneef L. Therapeutic outcome of prednisone medication and of orbital irradiation in patients with Graves' ophthalmopathy *Ophthalmologica* 1988, 197: 75–84
4 Hurbli T, Char DH, Haris J, Weaver K, Greenspan F, Shelline G. Radiation therapy for thyroid eye disease. *Am J Ophthalmol* 1985; 99: 633–7.
5 Mourits MPh, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy a novel approach. *Br J Ophthalmol* 1989; 73: 639–44
6 Dyer JA Ocular muscle surgery. In Gorman CA, Waller RR, Dyer JA, eds. *The eye and orbit in thyroid disease*. New York: Raven Press, 1984.
7 Werner SC Classification of the eye changes of Graves' disease. *J Clin Endocrinol Metab* 1969, 29: 982–4.
8 Crone RA. Motility disturbances in cases of endocrine exophthalmos In· Crone RA, ed *Diplopia* Amsterdam: Excerpta Medica, 1973: 350–60.
9 Fells P, McCany B. 'Fixed' versus 'adjustable' sutures in the treatment of dysthyroid ophthalmopathy In. Murube I, ed *Acta XVII Concilii Europaeae Strabologicae Associetatis* Madrid 1988 239–42.
10 Char DH Therapy of thyroid myopathy. In. Gardner JN, ed *Thyroid eye disease* Baltimore: Williams and Wilkins, 1985
11 Fletcher GH Clinical parameters *Textbook of radiotherapy.* Philadelphia Lea and Febiger, 1973· 133.
12 Koornneef L. Eyelid and orbital fascial attachments and their clinical significance. *Eye* 1988; 2: 130–4.

British Journal of Ophthalmology, 1990, 74, 484–485

Graves' ophthalmopathy: V. Aetiology of upper eyelid retraction in Graves' ophthalmopathy

Steven E Feldon, Lori Levin

Departments of Ophthalmology and Neurological Surgery, University of Southern California School of Medicine, and the Doheny Eye Institute, Los Angeles, California, USA
S E Feldon
L Levin

Correspondence to:
Dr Steven E Feldon,
Doheny Eye Institute, 1355
San Pablo Street, Los Angeles,
CA 90033, USA.

Accepted for publication
8 March 1990

Abstract

The volume of the levator superior rectus muscle complex was determined from computed tomography scans of 152 orbits from 76 patients with Graves' ophthalmopathy. Clinically observed lid retraction and lid lag did not correlate with the levator/superior rectus muscle volume and did not correlate with limitation of vertical eye movements or inferior rectus muscle volume. These results do not support previously published hypotheses that muscle hypertrophy or levator/superior rectus muscle overaction secondary to inferior rectus muscle restriction are major causes of lid retraction and lid lag. Local adhesion of the levator muscle to fixed orbital tissues is postulated to be the most likely basis for the characteristic lid retraction and lid lag of Graves' ophthalmopathy.

Retraction of the upper lid is a highly characteristic sign of Graves' ophthalmopathy. The retraction present in primary gaze is called Dalrymple's sign, and that present in down gaze (that is, lid lag) is called von Graefe's sign. Although most signs of Graves' ophthalmopathy can be attributed to inflammatory swelling and fibrosis of the extraocular muscles,[1] the pathophysiological basis for the lid retraction is not clear. Several possible causes have been suggested. Moses[2] supports the hypothesis advanced by Eden and Trotter[3] that overactivity of the sympathetic nervous system due to high levels of circulating thyroid hormone or another unidentified factor stimulates the tonus of the levator muscle, Müller's muscle, or both. Against this hypothesis of chemically induced muscle overaction is a lack of pupillary dilatation or other sign of sympathetic nervous system overactivity. Moreover, lid retraction often persists without hyperthyroidism. Levator overaction may also result from synkinetic activity related to the use of superior rectus muscles in overcoming inferior rectus restriction.[4] Grove[5] has reported on fatty infiltration between levator muscle and Müller's muscle, connective tissue proliferation forming adhesions to levator muscle, and degenerative changes within the levator muscle. He suggested that inflammatory changes with resultant enlargement and fibrosis of the levator muscle may cause the retraction.

Recently Small[6] reported that hypertrophy of individual muscle fibres contributed to the levator enlargement of Graves' ophthalmopathy. He proposed that this muscle hypertrophy caused 'hyperfunction' of the lid, leading to lid retraction. If Small's hypothesis is correct, then there should be a good correlation between quantitative measurements of superior rectus/levator muscle volume and clinical measures of lid retraction and lid lag. In the study described here this relationship between levator size and function is evaluated to determine possible pathophysiological mechanisms involved in lid retraction associated with Graves' ophthalmopathy.

Patients and methods

Computed tomographic scans of the orbits (0 to −15° angulation relative to the canthal meatal line) were obtained from 152 orbits of 76 patients with Graves' ophthalmopathy. The average age of the patients was 50·1 years (range 12 to 82); 14 were males and 62 females. All the patients were clinically euthyroid at the time of their evaluation. Other data from this patient group have been previously reported.[7]

A General Electric 9800 or General Electric 8800 computed tomographic scanner was available for performing the orbital scans. Non-overlapping, adjacent slices through the entire orbit (including roof and floor) were obtained in the axial plane at 1·5 mm intervals, except in nine patients in whom other intervals of 5 mm or less were used. The scans were imaged at window widths of 250 or 500 and at computed tomography numbers of 0 to +20 Hounsfield units. These were quantitatively analysed by an image analyser.[8] An attached pen enabled contours to be traced and digitised for analysis. Software provided with the image analyser was used to determine relative and absolute areas and volumes of structures by evaluating serial two-dimensional sections.

The volume of the superior muscles group included both levator and superior rectus muscle, as they could not be differentiated in the axial scan.

Lid retraction was measured as the amount of exposed sclera superior to the corneal limbus with the patient looking straight ahead. Lid lag was measured in a manner similar to lid retraction, but with the eyes directed downward. Up to 1 or 2 mm of possible lid retraction or lid lag were ignored in this operational definition in order to provide a constant landmark for quantitative measurement.

Results

Levator/superior rectus muscle volume was plotted against lid retraction and lid lag (Figs 1 and 2). A correlation performed between superior rectus/levator muscle volume and lid retraction resulted in coefficients of 0·02 with percentage total orbital volume, and 0·12 with absolute volume (see Table I). With lid lag as the clinical variable, correlation coefficients were

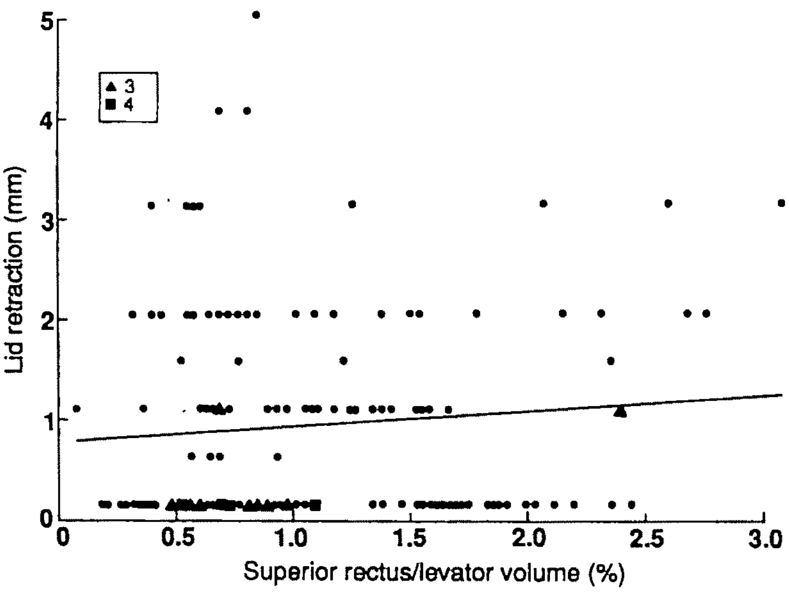


Figure 1 Superior rectus/levator muscle volume is expressed as a percentage of total orbital volume and plotted against lid retraction measured above the superior limbus. Diffuse scatter is demonstrated with almost no correlation. The solid line indicates least squares regression. Legend symbols indicate multiple overlapping points.

0·04 and 0·07. Similarly, low correlation coefficients (0·04 and 0·08) were obtained when lid retraction was tested against relative and absolute volume of the inferior rectus muscle. Correlations of inferior rectus muscle volume with lid lag resulted in coefficients of 0·09 and 0·01. Correlation coefficients between lid retraction or lid lag and limitation of vertical motility were 0·08 and 0·04, respectively. None of these values was statistically significant. By comparison, medial rectus volume did correlate with horizontal limitation of motility for this patient group with a coefficient of 0·54, and vertical limitations correlated with vertical muscle volumes with correlation coefficients between 0·33 and 0·38 (not shown in Table I).

Table 1 Correlation of lid findings with extraocular muscle volume and function

	Superior rectus/ levator volume		*Inferior rectus/ volume*		*Vertical limitation motility*
	%	*cm^3*	*%*	*cm^3*	
Lid retraction	0·02	0·12	0·04	0·08	0·08
Lid lag (mm)	0·04	0·07	0·09	0·01	0·04

Discussion

A significant correlation of extraocular muscle volume with extraocular muscle limitation has been shown in prior studies.[7,8] At first glance it seems somewhat surprising that lid retraction and lag do not correlate with enlargement of the involved muscle group. However, considering that the superior rectus/levator muscle group is usually substantially increased in volume only in advanced disease,[8] and that lid retraction/lag are often early signs, perhaps the absence of correlation should have been expected. These findings do not confirm the contention of Small[6] and of Frueh *et al*[9] that muscle hypertrophy and hyperfunction are related. The possibility that degenerative changes[5] or disinsertions of the levator[9] may counteract this relationship cannot be excluded.

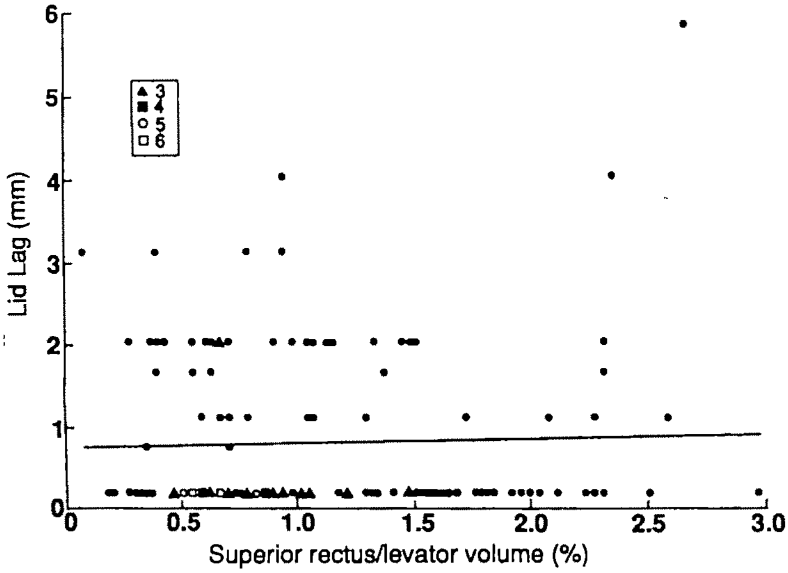


Figure 2 Superior rectus/levator volume (%) is plotted against lid lag (mm). See Figure 1 legend for further explanation.

Putterman and Urist[4] suggest that a synkinesis of the superior rectus and levator muscles to overcome inferior rectus restriction may frequently cause lid retraction. The lack of significant correlations between lid retraction and either clinical limitation of vertical motility or inferior rectus volume argues against their hypothesis.

Chemically mediated sympathetic nervous system overactivity with Müller muscle overaction may play a part in the development of lid retraction and lid lag, but in this study such sympathetic overactivity is not a consideration because all patients tested were clinically euthyroid.

On the basis of this study the explanation by Grove[5] indicating that lid retraction and lag may be related to adherence of the levator muscle to adjacent fixed orbital connective tissue and fat seems the most plausible. Such inflammatory changes may be independent of the levator muscle volume and are unrelated either to current thyroid status or to inferior rectus restriction. Of course in individual instances any or all of these possible causes of the observed lid changes may operate.

This work was supported in part by grant EY0 3908 from the National Institutes of Health, by an award from Research to Prevent Blindness Inc, New York, and by core grant EY0 3040 (Biometry Module)

1 Kroll AJ, Kuwabara T Dysthyroid ocular myopathy anatomy, histology, and electron microscopy. *Arch Ophthalmol* 1966; 76: 244–57
2 Moses RA. The eyelids In: Moses RA, Hart WM Jr, eds *Adler's physiology of the eye clinical application* St Louis Mosby, 1987 1-14.
3 Eden KC, Trotter WR Lid-retraction in toxic diffuse goitre *Lancet* 1942, ii 385–7
4 Putterman AM, Urist M. Surgical treatment of upper eyelid retraction *Arch Ophthalmol* 1972; 87: 401–5
5 Grove AS Jr Upper eyelid retraction and Graves' disease. *Ophthalmology* 1981; 88: 499–506.
6 Small RG Enlargement of levator palpebrae superioris muscle fibers in Graves' ophthalmopathy *Ophthalmology* 1989, 96: 424–30.
7 Hallin ES, Feldon SE. Graves' ophthalmopathy: II Correlation of clinical signs with measures derived from computed tomography. *Br J Ophthalmol* 1988; 72: 678–82.
8 Feldon SE, Weiner JM Clinical significance of extraocular muscle volumes in Graves' ophthalmopathy. a quantitative computed tomography study. *Arch Ophthalmol* 1982, 100 1266–9.
9 Frueh BR, Musch DC, Garber FW Lid retraction and levator aponeurosis defects in Graves' eye disease. *Ophthalmic Surg* 1986; 17: 216–20.

British Journal of Ophthalmology, 1990, 74, 486–489

Stabilisation of refraction following extracapsular cataract extraction

P Baranyovits

Wolverhampton and Midland Counties Eye Infirmary, Compton Road, Wolverhampton WV3 9QR
P Baranyovits

Correspondence to:
P Baranyovits, FRCS

Accepted for publication
15 March 1990

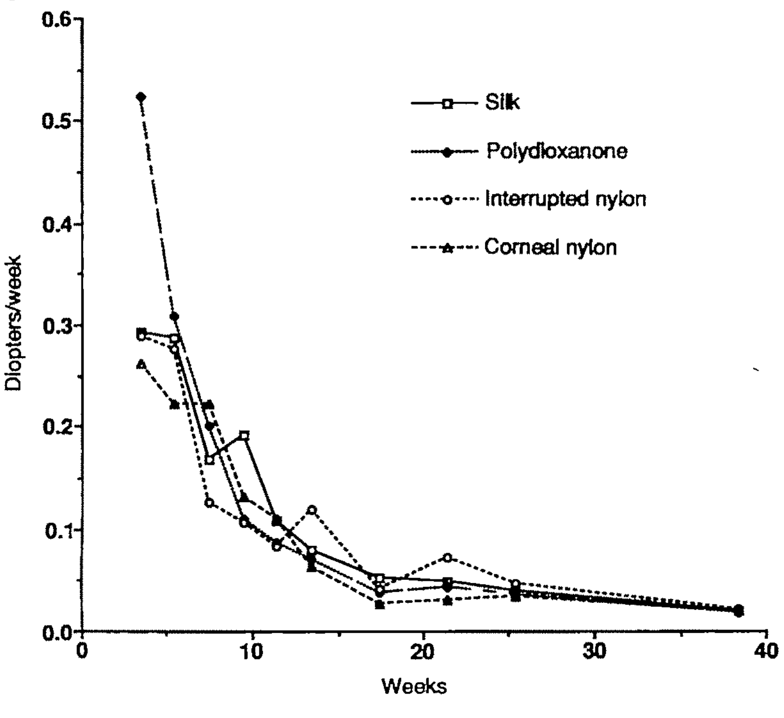
Abstract

Regular serial refraction was used to determine the rate of stabilisation of refraction following routine extracapsular cataract surgery in 85 eyes. Patients were divided into four groups depending on wound closure technique: limbal section closed by interrupted 8–0 virgin silk, 9–0 polydioxanone or 10-0 nylon sutures, and corneal section closed by continuous 10–0 nylon suture. Stabilisation of refraction, sufficient to prescribe satisfactory glasses, occurred at three months except in the interrupted 10–0 nylon group, when stabilisation was delayed to between four and five months. The factors affecting stabilisation and the causes of the differences observed are discussed.

The prescription of 'first glasses' following cataract surgery is usually undertaken after a fixed and often arbitrary period, as frequent serial refractions are not practical in most busy outpatient departments. Glasses prescribed too soon may cause disappointment and unnecessary expense; if prescribed too late they may prolong disability and frustration.

Changes in refraction following cataract surgery have been recognised for over a century. Many workers have investigated postcataract astigmatism. The effects of the following factors have been studied: type,[1-4] depth,[5] and number[6] of sutures, pre- or postplaced sutures,[6] wound placement,[7] and size of wound.[8] More recently techniques of modifying postcataract astigmatism by choice of incision[9] and suture adjustment[10] or removal[11 12] have all been considered. Changes of corneal curvature as a function of time have been investigated, but the actual rate of stabilisation of the cataract wound has received less attention.

Figure 1 Rate of change of sphere.



In 1950 Floyd[13] reported on 47 eyes following cataract surgery with Graefe section and two sutures. Follow-up by monthly keratometry for six months suggested 'significant' changes in corneal curvature for at least three months after surgery. Gill[14] in 1972 followed up 1500 postoperative cataract patients; they had intracapsular extractions closed with gut, silk, or nylon, and keratometry was performed at unspecified intervals for up to one year. All groups showed a decay in the initial with-the-rule astigmatism persisting for at least six months. In 1984 Reading[8] reported on 43 eyes undergoing intracapsular cataract extraction sutured with virgin silk. These patients were followed up at monthly intervals for one year by photokeratometry. Changes in corneal curvature after one month were found to be 'small'.

In 1988 we reported[15] on 47 eyes following intracapsular cataract extraction at Wolverhampton. Patients were divided into two groups: sections were closed either with interrupted 8–0 virgin silk or continuous 9–0 nylon. Refraction was performed every two weeks for the first three months and then at monthly intervals. The results suggested that stability sufficient to prescribe glasses was achieved at three months in the silk group and four months in the nylon group.

Recently there have been several long-term studies[4 12 16] in which the period of follow-up extended for up to five years. Extracapsular cataract extraction was performed with a posterior chamber intraocular lens (IOL), and sections were sutured with nylon, polypropylene (Prolene), or polyester (Mersilene). Relatively large numbers of patients were included, but follow-up was at rather infrequent intervals. All groups showed a decay of the initial with-the-rule astigmatism, which persisted for up to three years. Cravy,[4] reporting on 395 patients, found 'initial stabilisation' at one month in the 10–0 nylon group but suggested that glasses may need to be changed up to four times in the first year. Axt,[16] reporting on 500 cases with sections closed by 10–0 interrupted nylon and continuous 8–0 polyglactin (Vicryl), found the greatest changes during the first six months and that 'permanent' glasses could be prescribed at between nine and 12 months.

This prospective study was undertaken to monitor refraction changes occurring during the first nine months after the smaller sections of extracapsular surgery. The aim was to determine when stability is sufficient to prescribe 'first glasses,' as complete stability may not be achieved for several years after surgery. Other questions considered were whether the rate of stabilisation is consistent in different patients and whether it is influenced by closure technique, age, or the degree of immediate postoperative astigmatism.

Material and methods

PATIENTS

From the beginning of this prospective study all patients undergoing uncomplicated extracapsular cataract extraction were included provided they were able, co-operative, and had no other serious ocular disease. A total of 81 patients, 81 eyes, were followed up for nine months. The total included 48 women (average age 73·3 years, 95% confidence interval 2·6) and 33 men (average age 67·1 years, 95% confidence interval 3·0).

SURGERY

On a consecutive basis patients were divided into four groups: Group A: limbal incision, closure with 5 interrupted 9–0 virgin silk sutures (20 eyes). Group B: limbal incision, closure with 5 interrupted 9–0 polydioxanone (PDS) sutures (20 eyes). Group C: limbal incision, closure with 5 interrupted 10–0 nylon sutures (20 eyes). Group D: corneal section, closure with continuous 10–0 nylon suture (21 eyes).

Groups A, C, and D were included because they were the three closure techniques commonly used in the Wolverhampton Eye Infirmary and many other hospitals. Group B, interrupted 9–0 polydioxanone sutures (PDS), was included because it is a new type of suture becoming available to the ophthalmologist. Polydioxanone is a synthetic suture material which is absorbed by hydrolysis; its half life in tissue is 28 days[17] (that is, loss of half tensile strength). In the 9–0 form polydioxanone is a monofilament. Three different surgeons performed the operations using a similar microsurgical technique. Limbal incisions extended approximately 120° and corneal sections approximately 140°. Extracapsular cataract extraction was then performed following routine anterior capsulotomy or by intercapsular technique. The nucleus was expressed and remaining cortex aspirated by coaxial cannula. A J-loop posterior chamber lens was then inserted into the capsular bag. Patients were allocated in rotation to the four groups described above. All patients were prescribed a topical steroid (betamethasone 0·1%) four times a day for three weeks; this was then reduced and discontinued over the following four weeks.

FOLLOW-UP

All patients were followed up by the author for nine months. Refraction was performed during the first week after surgery and repeated at two-weekly intervals for three months, thereafter monthly for a further three months. The final refraction was performed at nine months. All refractions were carried out with the same equipment, ensuring a constant back vertex distance. Retinoscopy was followed by subjective refraction; the sphere was confirmed by the duochrome test and the cylinder and axis by using Jackson's cross cylinder.

Serial refractions were analysed and stabilisation times were compared over values of the independent variables by means of analysis of variance (ANOVA). In the case of significant relationships linear contrasts were used to identify the source of significance.

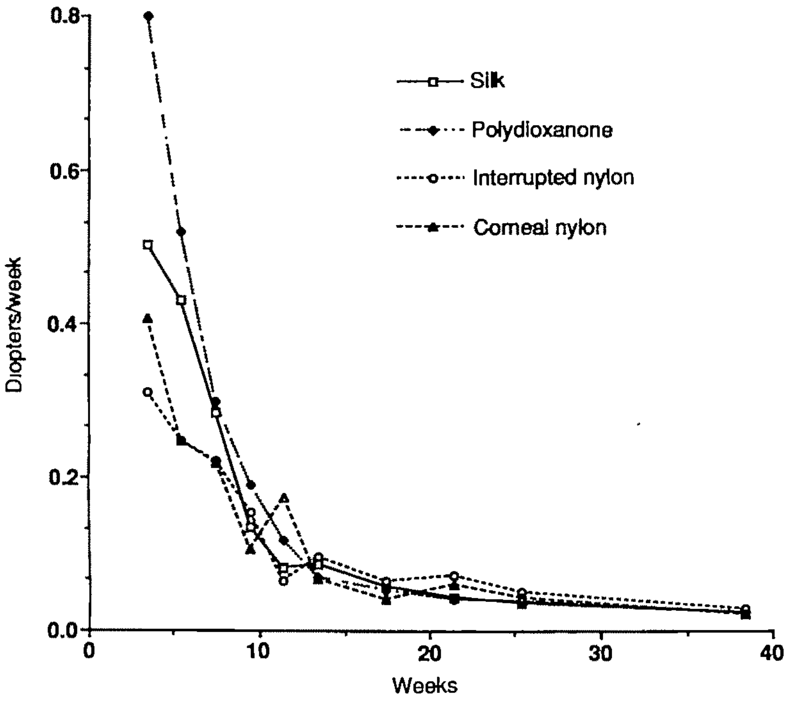
Results

The rate of change of each component of refraction was calculated from the serial refractions of each patient. The units of change were dioptres/week and degrees/week. The mean rate of change at all time intervals was calculated for each suture group and is presented graphically in Figures 1, 2 and 3.

The 'absorbable' suture virgin silk and polydioxanone showed an initial rapid change in refraction, particularly with the cylinder and axis component. This was associated with the rapid change from with-the-rule astigmatism to against-the-rule occurring at approximately five weeks in both the silk and polydioxanone groups. At nine months 100% of eyes in the silk group and 91% of eyes in the polydioxanone group had against-the-rule astigmatism. The decay of the induced with-the-rule astigmatism in the nylon suture groups was more gradual: at nine months 55% of eyes in the interrupted nylon group and 64% of eyes in the corneal section group had developed against-the-rule astigmatism. These results are displayed in the Table.

The prescribing time was estimated retrospectively for each patient. For the purposes of this study this was taken to be the time after surgery that the refraction was judged to be sufficiently stable to allow the satisfactory prescription of

Figure 2 Rate of change of cylinder.



glasses. The refraction results for the full nine months were reviewed, and the prescribing time was taken to be the earliest time that the refraction approached the 'final' nine-month result. The criteria used were fairly strict – a maximum difference of 0·5 dioptre in sphere, 0·25 dioptre in cylinder, and 5° in axis. The results are displayed in the Table and graphically in Figure 4. The mean prescribing time for groups A, B, and D is in the region of three months and for group C (interrupted 10–0 nylon) between four and five months. These results are similar to our findings with the larger sections in intracapsular cataract extractions.[15]

Analysis of variance showed a significant difference between the suture groups ($p=0·020$). The source of significance was the prolonged prescribing time in group C ($p=0·003$). Greater variation in prescribing time was found in both nylon groups (C and D) than in the absorbable suture groups (A and B). Finally no significant correlation was demonstrated between patient age, initial corneal distortion (initial cylinder), and rate of stabilisation.

Discussion

All the eyes included in this study showed a decay of surgically induced with-the-rule astigmatism. This process is well recognised and described in many other studies.[4 9 12 18 19] Recent long-term studies have shown that this astigmatism decay may continue for two to three years before complete stabilisation of the cataract wound.

The major influence in this characteristic change in astigmatism is the complex relationship between suture and wound healing. Relaxation of the tissue, compressed by sutures along the incision, occurs owing to a loss of tensile strength in the suture, loosening of knots, or the suture cutting through the tissue. This may restore the preoperative corneal curvature, though the relaxation of tissue across the wound does not necessarily coincide with the wound's achieving strength sufficient to prevent its stretching. Significant wound stretching may continue the process of decay of induced astigmatism beyond the preoperative corneal curvature resulting in against-the-rule astigmatism.

The speed of wound healing in the cornea and limbal area is very slow. In 1969 Flaxel and Swan[20] reported on 18 post-mortem eyes obtained at varying times after cataract surgery. They found that initial fibrovascular invasion of the wound was complete at two weeks, but this provided very little strength. The increase in strength of the limbal wound depends on the restoration of the collagen structure. Wound remodelling was first seen in a 46-day specimen and was complete by 2·5 years. In 1968 Gassel and Dohlman[21] reported on the tensile strength of limbal and corneal wounds in rabbits. Again healing was found to be very slow.

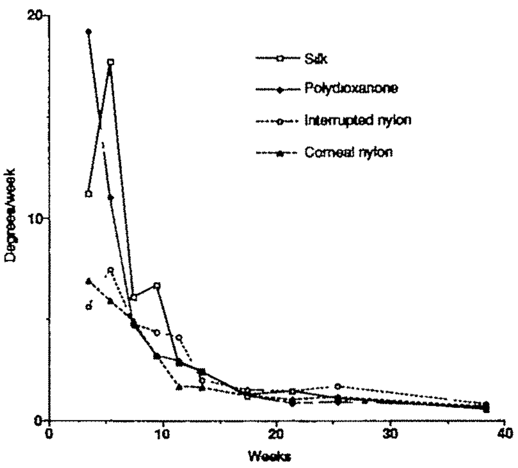


Figure 3 Rate of change of axis.

The absorbable suture polydioxanone and virgin silk, which behaves in a similar manner, lose their apparent tensile strength at between five and six weeks. This can be seen as a rapid change in astigmatism in Figures 2 and 3. After this period there is a more gradual decay of surgically induced with-the-rule astigmatism, and most of the sutures, particularly polydioxanone, are absorbed or extruded by six months. This being the case, suture tension is soon lost as a factor influencing the stabilisation of refraction in groups A and B. Hence, wound strength remains as the only major variable in this simplified equation. One would then expect that eyes sutured with an absorbable material would stabilise at a rate directly related to wound healing and therefore more quickly and consistently, because there are no prolonged influences on the wound. The results from this study support this, though the difference in prescribing time between the absorbable suture groups and the corneal continuous nylon group was not significant. The degree of variation in the mean prescribing times of both absorbable sutures (A and B) were less than the nylon groups (C and D).

The corneal section group, sutured with continuous nylon, had a mean prescribing time only slightly longer than the absorbable suture groups but significantly less than the limbal interrupted nylon group. It is unlikely that the position of the section (limbal versus corneal) contributes much to this difference, as a similar difference exists between suture groups A and B and group C (all limbal sections). Moreover the rate of wound healing can be expected to be similar, if not greater, in the more peripheral wound.[21] The remaining difference between groups C and D is the suture technique (continuous versus interrupted nylon). By virtue of the interconnecting segments of suture in the continuous group the tension in each 'bite' will show less variation than the individual sutures in the interrupted group. Hence the loss of tension that occurs in a continuous suture postoperatively should allow decay in the induced surgical astigmatism with a more stable axis. Loosening of an interrupted non-absorbable suture is likely to be unrelated to its neighbours, resulting in erratic shifts of axis. Figure 3, showing rate of change of axis, appears to support this view, while Figures 1 and 2 showing rate of change of sphere and cylinder, are more similar.

An ideal suture for conventional cataract surgery would maintain its tensile strength long enough to allow the healing wound to reach sufficient strength to prevent significant stretching when unsupported. This should be in the

Table 1 Refraction results for each wound closure group

95% Confidence interval in brackets	*Group A (silk)*	*Group B (PDS)*	*Group C (interrupted nylon)*	*Group D (corneal nylon)*
Number of eyes	21	22	20	22
Mean initial cyl	2·64 D (0·49)	2·74 D (0·53)	2·99 D (0·49)	2·65 D (0·64)
%With-the-rule	95%	100%	100%	82%
Mean final cyl	2·45 D (0·39)	2·11 D (0·44)	1·9 D (0·34)	2·03 D (0·38)
%Against-the-rule	100%	91%	55%	64%
Nine-month decay of surgically induced astigmatism	5·07 D (0·74)	4·72 D (0·49)	3·24 D (0·89)	2·84 D (0·89)
Mean prescribing time	12·9 wks (2·5)	13·4 wks (2·2)	18·7 wks (2·9)	14·6 wks (3·0)

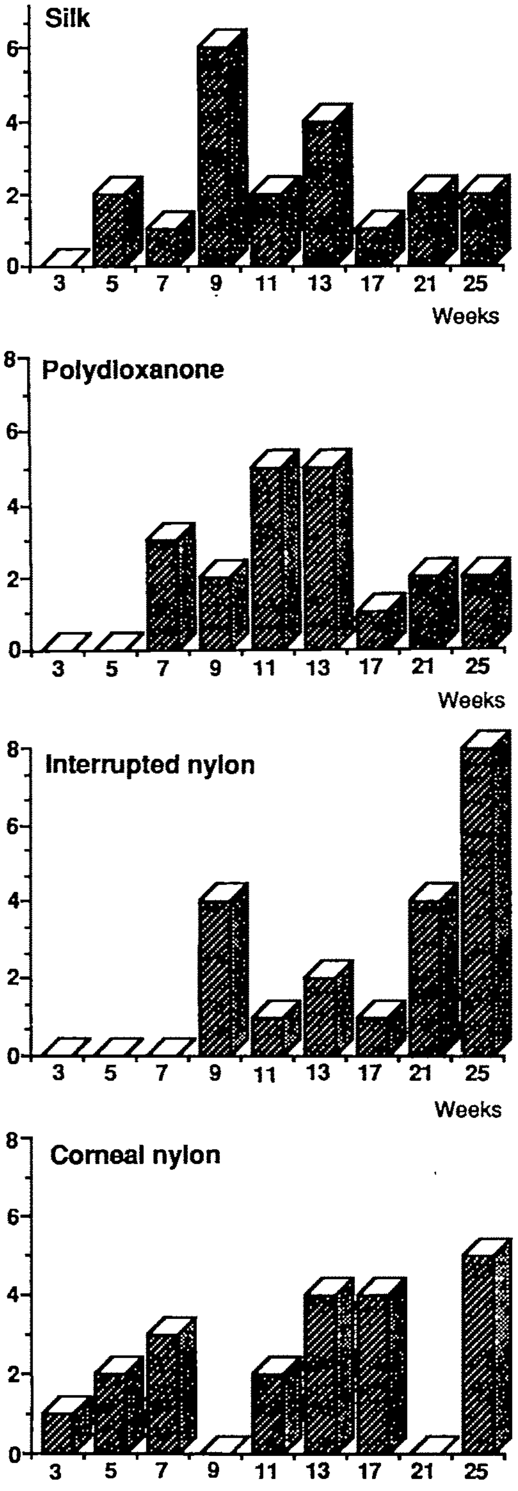


Figure 4 Graphs showing when patients reach stable refraction following extracapsular cataract extraction in each wound closure group.

region of 12 to 14 weeks, which is the mean stabilisation time range for polydioxanone and silk groups (in effect by this time these wounds are unsupported). The ideal suture should then be absorbed to avoid further influencing wound stabilisation. An alternative solution would be to use a non-absorbable material and remove or cut all sutures at a similar time. The rate of wound healing is the key to stabilisation. Hence procedures that may delay this process should also be avoided, such as excessive cautery and prolonged use of steroids.

Recent studies[4 12 16] have shown that complete stabilisation of refraction does not occur until two to three years after cataract surgery. As one would not expect patients to wait this long for their first glasses, they should be prescribed when the rate of refraction change is considered slow enough to be acceptable. For the purposes of this study the prescribing time was calculated by rigid criteria in order to demonstrate differences between suture groups and the degree of variability. In practice this prescribing time, which is no more than a mean for a particular surgical technique, should be used only as a guide. Not only does it show considerable variability but there are several other factors to consider with the individual patient. These would include vision in the fellow eye, potential vision in the operated eye, degree of refractive error, urgency of rehabilitation, and the patient's wishes. However, with better understanding of the behaviour of post-cataract refraction, these many factors may be weighted appropriately when judging when to prescribe 'first glasses.'

1 Pearce JL Discussion on suture material *Adv Ophthalmol* 1970; 22: 58–9.

2 Wyman GJ Comparison of results. 100 cases with 8–0 silk versus 100 cases with 9–0 – 10–0 nylon In Emery JM, Paton D, eds. *Current concepts in cataract surgery* St Louis Mosby, 1974 91–2

3 Stainer GA, Binder PS, Parker WT, Perl T The natural and modified course of post-cataract astigmatism *Ophthalmic Surg* 1982, 13: 822-7

4 Cravy TV. Long-term corneal astigmatism related to selected elastic, monofilament, nonabsorbable sutures *J Cataract Refract Surg*, 1989; 15: 61–9

5 Van Rij G, Waring GO Changes in corneal curvature induced by sutures and incisions *Am J Ophthalmol* 1984, 98: 773–83

6 Singh D, Kumar K Keratometric changes after cataract extraction *Br J Ophthalmol* 1976; 98: 638–41

7 Thrasher BH, Boerner CF Control of astigmatism by wound placement. *J Am Intraocul Implant Soc* 1984, 10: 176–80

8 Reading VM Astigmatism following cataract surgery *Br J Ophthalmol* 1984, 68: 97–104

9 Maloney WF, Grindle L, Sanders D, Pearcy D. Astigmatism control for the cateract surgeon A comprehensive review of surgically tailored astigmatism reduction *J Cataract Refract Surg* 1989, 15: 45–54.

10 Atkins AD, Roper-Hall MJ Control of postoperative astigmatism. *Br J Ophthalmol* 1985; 69: 348–51

11 Kronish JW, Forster RK. Control of corneal astigmatism following cataract extraction by selective suture cutting *Arch Ophthalmol* 1987, 105: 1650–5

12 Richards SC, Brodstein RS, Richards WL, Olson RJ, Combe PH, Crowell KE Long-term course of surgically induced astigmatism *J Cataract Refract Surg* 1988; 14: 270–6

13 Floyd G. Changes in corneal curvature following cataract extraction. *Am J Ophthalmol* 1951, 34: 1525–33.

14 Gills JP. The effect of cataract sutures on postoperative astigmatism *Am J Optom Physiol Opt* 1974; 51: 97–100

15 Baranyovits PR Stabilisation of refraction following cataract surgery *Br J Ophthmol* 1988; 72: 815–9

16 Axt JC Longitudinal study of postoperative astigmatism *J Cataract Refract Surg* 1987; 13: 381–8

17 Batholomew RS PDS (polydioxanone suture) a new synthetic absorbable suture in cataract surgery. *Ophthalmologica* 1981, 183: 81–5

18 Cory CC. Prevention and treatment of postimplantation astigmatism *J Cataract Refract Surg* 1989, 15: 58–60

19 Jampel HD, Thompson JR, Baker CC, Stark WJ A computerised analysis of astigmatism after cataract surgery *Ophthalmic Surg* 1986, 17: 786–90

20 Flaxel JT, Swan KC. Limbal wound healing after cataract extraction. *Arch Ophthalmol* 1969; 81: 653–9

21 Gasset AR, Dohlman CH The tensile strength of corneal wounds. *Arch Ophthalmol* 1968; 79: 595–602

British Journal of Ophthalmology, 1990, 74, 490–493

Incidence of inadvertent globe perforation during strabismus surgery

R J Morris, P H Rosen, P Fells

Abstract

Visual loss following strabismus is rare and usually follows inadvertent perforation of the globe at the time of surgery. Previous studies have reported that the incidence of this complication occurs in 8% to 12·1% of patients undergoing conventional strabismus surgery, and higher incidences have been reported for posterior fixation sutures. We conducted a prospective study to determine the incidence of this complication in our patients. We identified one case of globe perforation in 67 patients (100 eyes). Twenty-two patients (44 eyes) had undergone previous strabismus surgery, and there was no evidence of previous scleral perforation in this group. We discuss the recent advances in strabismus surgery which may account for this difference in the incidence of scleral perforation.

Inadvertent perforation of the globe is a recognised complication of strabismus surgery. It usually occurs during intrascleral passage of needles and may involve the sclera, choroid, or retina.[1] It has been reported when disinserting a muscle from the globe and may also occur when passing sutures through a muscle prior to its disinsertion.[1] In the majority of cases scleral perforation is undetected at the time of surgery and discovered later by the presence of a chorioretinal scar, which may represent deep choroidal involvement rather than actual retinal perforation.

Sequelae leading to visual loss are rare and include retinal detachment, endophthalmitis, posterior chamber haemorrhage, cataract, lens dislocation, hyphaema, and glaucoma.[2–11] Reports of the estimated incidence of retinal detachment in strabismus surgery vary from less than 1 in 10 000[12] to 1 in 37 000.[8] The reported incidence of endophthalmitis has varied from 1 in 3500[8] to 1 in 8000,[13] but Locatcher-Khorazo and Seegal did not find one case in 12 263 cases of strabismus surgery reviewed.[14]

As the majority of cases of scleral perforation are minor and produce no complications, the true incidence of scleral perforation is not well established. It has been reported as occurring in 8%,[15] 9·2%,[3] and 12·1%[16] of patients during standard strabismus surgery, and higher incidences are described for posterior fixation sutures.[17 18] Inadvertent scleral perforation was not identified at the time of surgery in any of these studies. Mittleman and Bakos[12] predicted that, if the incidence of this complication is 9·2%, as reported by Gottlieb and Castro,[3] then in the United States there would be an incidence of 7600 globe perforations a year.

These retrospective studies were reported before the widespread use of modern suture materials and needles in strabismus surgery, and it was our impression that with the use of modern surgical techniques the incidence of scleral perforations was much lower than previously reported. To try to establish the incidence of globe perforation in our patients we conducted a prospective study in consecutive patients undergoing strabismus surgery.

Material and methods

Sixty-seven consecutive patients undergoing strabismus surgery in the six-month period October 1988 to March 1989 were included in the study. There were 33 males and 34 females, and the age range was from six months to 52 years (mean 11·2 years).

Prior to surgery the pupils of the operated eyes were dilated with cyclopentolate hydrochloride 1% and phenylephrine hydrochloride 2·5%. Fundal examination was performed by indirect ophthalmoscopy and scleral indentation, and any chorioretinal abnormalities noted. After surgery and before suturing the conjunctiva the retina was re-examined over the site of each scleral suture by the indirect ophthalmoscope in order to identify any chorioretinal haemorrhages, retinal tears, or vitreous haemorrhage indicative of inadvertent scleral perforation. The suture knot was held with a fine Colibri forceps so that gentle scleral indentation could be applied directly over the site of the scleral passage of the needle. In those cases with posterior fixation sutures this was not always possible, and the globe was gently indented with a squint hook over the site of the suture.

SURGICAL TECHNIQUE

Surgery was performed with the operating microscope. All extraocular muscle surgery was performed with limbal conjunctival incisions. The muscle insertion was directly visualised before isolating it on a squint hook, and the muscle was then cleaned of its fascial attachments and the intermuscular septum.

Muscle recessions. A single armed 6-0 Vicryl (polyglactin 910) suture on a three-eighths circle spatulate needle was passed through the muscle tendon from the centre to each border and lock bites taken to incorporate the outer one-third of the muscle tendon. The muscle was disinserted from the globe with Wescott scissors and haemostasis secured by bipolar cautery. The muscle was then reattached to the globe at the appropriate distance behind its original insertion. Scleral bites were passed from the outer border of the muscle tendon towards the centre, and the suture was tied to its free end; the second suture

Moorfields Eye Hospital, City Road, London EC1V 2PD
R J Morris
P H Rosen
P Fells

Correspondence to:
P H Rosen, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Accepted for publication
8 March 1990

was then reattached in the same way. The inferior oblique muscle was recessed to a position 3 mm posterior and 3 mm lateral to the lateral border of the inferior rectus by a single suture through the anterior border of the muscle.

Muscle resections. The muscle was identified and cleaned in the same way as for a recession. Two Chavasse muscle hooks were then placed under the muscle and two single armed 6-O Vicryl sutures, on a three-eighths circle spatulate needle, placed through each border of the muscle, with lock bites being taken to secure the suture. The muscle was resutured to the globe at the original insertion. If there was any bowing of the insertion another suture was placed through the central portion of the muscle.

Faden procedure. The technique used for Faden sutures has been described in a previous paper from Moorfields Eye Hospital.[18]

Muscle transposition procedures. The vertical recti were identified and two 6-O Vicryl sutures passed through the tendon, as in a muscle recession, and the muscle was fully transposed laterally.[19] In one case the horizontal recti were transposed inferiorly by a similar technique.

Results

The diagnosis at presentation in the 67 patients undergoing strabismus surgery can be seen in Table I.

One hundred and thirty-seven muscles in the 67 patients (100 eyes) underwent surgery. One hundred and thirty-four required resuturing to the globe; the remaining three muscles underwent superior oblique tenotomy (Table II). In only one patient did inadvertent perforation of the globe occur at the time of surgery. This occurred in a five-year-old boy with right Duane's syndrome (type I). One year previously he had undergone a right medial rectus recession of 5 mm and right lateral rectus resection of 5 mm at another institution. In order to correct reduced abduction associated with a persistent abnormal head posture a temporal transposition of the vertical recti in the right eye was performed. Scleral perforation was suspected during the procedure when the medial border of the superior rectus muscle was resutured to the globe, though there was no prolapse of uveal tissue or vitreous. This was subsequently confirmed at the end of the procedure by indirect ophthalmoscopy, when a small deep retinal haemorrhage was identified at the site of suture placement. This was not associated with a retinal hole or vitreous haemorrhage, and no transcleral cryotherapy was therefore applied to the site. No complications developed over a six-month follow-up.

Prior to inclusion in the study 22 patients (44 eyes) had previously undergone strabismus surgery: 17 on one occasion, 4 on two occasions, and 1 on three occasions. The total number of muscle procedures in which the muscle had been resutured to the globe was 60. In addition, one patient had an injection of botulinum toxin to the medial rectus five days before temporal transposition of the vertical recti for a sixth nerve palsy. In none of these patients was there any chorioretinal scarring to suggest previous ocular perforation.

Table 1 Diagnosis at presentation

Diagnosis	*No of patients*
Esotropia	37
Exotropia	11
IV nerve palsy	6
Duane's syndrome	4
VI nerve palsy	6
Blow-out fracture	1
Thyroid eye disease	1
Congenital nystagmus	1

Discussion

Strabismus surgery is one of the commonest procedures performed by the general ophthalmologist. Although the risk of visual loss is remote, it is usually related to perforation of the globe at the time of surgery,[20] and every precaution should be taken to keep this risk to a minimum.

In the 67 patients (100 eyes) studied prospectively, we identified only one case of scleral perforation in the 134 procedures in which the muscle was reattached to the globe. In this case the perforation was suspected at the time of suture placement and confirmed by the presence of a small deep retinal haemorrhage on fundal examination. No evidence of scleral perforation was found in the 22 patients who had had previous muscle surgery. In total only one scleral perforation was identified in 194 muscle procedures (144 eyes). This incidence of scleral perforation is lower than previously described. Although Gottleib and Castro reported an incidence of 9·2% in their series, they did not state whether the 68 patients recalled was the total number of patients operated on over a five-year period or only those who attended for re-examination.[3] Kaluzny *et al* in their retrospective study recalled 91 patients operated on over an eight-year period and report an incidence of 10·2% in 108 eyes operated upon.[16] In both these studies it is not clear if the figures represent a true incidence of consecutive patients operated on or only the incidence in those patients they examined. Rojas *et al*,[15] however, reported on consecutive patients but did not examine the fundus before surgery, and, as in the other studies, they included any retinal or choroidal abnormality as indicative of perforation. Therefore it is possible that the reported figures

Table 2 Surgical procedures

Patients	67
Eyes	100
Muscles	
Recessions	
Medial rectus	50
Inferior oblique	14
Lateral rectus	14
Inferior rectus	3
Resections	
Lateral rectus	24
Medial rectus	8
Faden	
Lateral rectus	9
Medial rectus	2
Transposition procedures	6
Modified Harada Ito	2
Faden with recession	
Medial rectus	2
Superior oblique tenotomy	3

overestimate the incidence of globe perforation. Nevertheless we consider these figures are unacceptly high and that with appropriate precautions and careful surgical technique a lower incidence of complications can be achieved.

It is well documented that the sclera is thinnest (0·3 mm) behind the insertion of the rectus muscles and thicker (0·6 mm) at the muscle insertions.[21] Scleral perforation is commoner during muscle recessions than resections.[22] Mills *et al*[22] and Capó *et al*[23] have recommended the use of hang-back sutures to reduce the risk of scleral perforation during standard muscle recessions. This procedure has the theoretical disadvantage that the recessed muscle may creep forwards or slip, causing vertical deviations. However, perforation has been reported after muscle resections[3,9,15] and during suture placement at the original muscle insertion for adjustable sutures.[7] In Gottleib and Castro's series[3] four of the 10 patients developed perforation as a result of muscle resections, and in none of these patients did they describe which suture material or needle was used. Globe perforation has also been reported as the sutures are passed through the muscle before the globe is disinserted.[5,10] and may occur during disinsertion of the muscle from the sclera.[1] Although the sclera is thinner behind the insertion of the rectus muscles, it is clear that this is not the only factor associated with scleral perforation.

We suggest that all strabismus surgery should be performed with some form of magnification, either with the operating microscope or with spectacle mounted loupes. The operating microscope provides excellent lighting and magnification, but does reduce the field size and depth of focus and restrict the surgeon's mobility. With loupes a headlight affords excellent lighting as an alternative to the standard overhead operating room lights.

When dissecting tissues in order to isolate muscles it is important to directly visualise tissues before using sharp dissection, particularly in the presence of scar tissue in reoperations and in restrictive conditions such as thyroid eye disease. Before disinserting a muscle or passing a suture through the sclera it is essential to ensure good haemostasis and adequate exposure, by means of a Fison or Desmarres retractor if necessary. When a muscle is reattached, the needle should be placed through the superficial ⅓ to ½ of the scleral thickness and passed tangential to the sclera, with the tip visible at all times. Magnification enables direct visualisation of the intrascleral course of the needle as well as the intrascleral course of the vortex veins.

The most commonly used suture material in strabismus surgery is now 6–0 Vicryl (polyglactin 910).[24] It has the advantages of causing minimal tissue reaction, having a high tensile strength, good knot holding ability, and a predictable absorption rate, but has the disadvantage of adhering to tissues.[25] Its high tensile strength allows 6-O sutures to be used with small needles. Our preference is to use a fine spatulate needle which cuts tissue at the sides and tip. Other spatulate needles with a point below lead to a deeper bite than those with a point above and are more likely to cause scleral perforation.[26] Provided the edges of the needle are parallel to the sclera during its intrascleral course the risk of inadvertent perforation is low. We use a three-eighths circle spatulate needle, but in some situations where access is difficult a half circle spatulate needle can be advantageous. It has the disadvantage of allowing a shorter scleral bite, but of the same depth as a three-eighths circle needle.[26] A reverse cutting needle has a cutting edge on the convex surface and therefore has a theoretically greater risk of causing scleral perforation. However, some surgeons prefer it, as, unlike the wider spatulate needles, it does not have to remain exactly parallel to the scleral surface during its intrascleral course.[27] Posterior fixation sutures are inserted postequatorially on larger needles where the sclera is thin and access difficult; this is the likely explanation for the higher incidence of scleral perforations with this procedure.

The management of such perforations is controversial. Some authors recommend that they should be treated with transcleral cryotherapy regardless of the depth of perforation, to reduce the incidence of retinal detachment.[3,5,9] Mittleman and Bakos, however, in animal experiments found a higher incidence of retinal detachment associated with heavy retinal cryotherapy, and they suggest that unless intravitreal haemorrhage occurs or the patient has a predisposing risk factor for retinal detachment no treatment is indicated.[12] Retinal detachment may be secondary to vitreous traction and presentation delayed, so that patients with globe perforation complicating strabismus surgery should be followed up long term. If scleral perforation is detected at the time of surgery, conjunctival cultures should be obtained and antibiotics without steroids administered because of the small risk of endophthalmitis. Such patients should be followed up closely for signs of infection in the early postoperative period.

1 Wagner RS, Nelson LR Complications following strabismus surgery. *Int Ophthalmol Clin* 1985; 25: 171–8

2 McLean JM, Galin MA, Baras I. Retinal perforation during strabismus surgery *Am J Ophthalmol* 1960; 50: 1167–9

3 Gottleib FG, Castro JL. Perforation of the globe during strabismus surgery. *Arch Ophthalmol* 1970, 84: 151–7.

4 Apple DJ, Jones GR, Reidy JJ, Loftfield K. Ocular perforation and phthisis bulbi secondary to strabismus surgery. *J Pediatr Ophthalmol Strabismus* 1985. 22: 184–7

5 Salamon SM, Friberg TR, Luxenberg MN. Endophthalmitis after strabismus surgery. *Am J Ophthalmol* 1982, 93: 39–41

6 McNeer KW. Three complications of strabismus surgery. *Ann Ophthalmol* 1975; 7: 441–6.

7 Greenberg DR, Ellenhorn NL, Chapman LI, Miller MT, Folk ER Posterior chamber haemorrhage during strabismus surgery. *Am J Ophthalmol* 1988; 106: 634–5

8 Knobloch R, Lorenz A Uberernste Komplikationen nach Schieloperationen. *Klin Monatsbl Augenheilkd* 1962; 141: 348–353

9 Basmadjian G, Labelle P, Dumas J Retinal detachment after strabismus surgery *Am J Ophthalmol* 1975; 79: 305–9

10 Hittner HM. Lens dislocation after strabismus surgery. *Ann Ophthalmol* 1979, 11: 1115–9.

11 Hanver WH, Kimball OP. Scleral perforation during strabismus surgery *Am J Ophthalmol* 1960; 50: 807–8

12 Mittleman D, Bakos IM The role of retinal cryopexy in the management of experimental perforation of the eye during strabismus surgery. *J Pediatr Ophthalmol Strabismus* 1984, 21: 186–9

13 Weinstein R, Mondino BJ, Weinberg RJ, Biglan AW. Endophthalmitis in the pediatric population. *Ann Ophthalmol* 1979; 6: 935–43.

14 Locatcher-Khorazo D, Seegal BC. *Microbiology of the eye.* St Louis: Mosby, 1972: 74.

15 Rojas B, Vargas A, Riveros M. Retinal periphery after strabismus surgery *Arch Chil Oftalmol* 1979, 36: 119–21.

16 Kaluzny J, Ralcewicz H, Perlikiewicz-Kikielowa A Eye fundus periphery after operation for squint. *Klin Oczna* 1977, 47: 557–8.

17 Alio JL, Faci A. Fundus changes following Faden operation *Arch Ophthalmol* 1984; **102:** 211–3

18 Lyons CJ, Fells P, Lee JP, MacIntyre A. Chorioretinal scarring after the Faden operation a retrospective review of 100 procedures. *Eye* 1989, **3:** 401–3.

19 Fitzsimmons R, Lee JP, Elston J. Treatment of sixth nerve palsy in adults with combined botulinum toxin and chemodenervation and surgery. *Ophthalmology* 1988; **95:** 1535–42.

20 Simon JW, Dannemann AF, Hampton GR, Richards R 'Which eye will you be straightening, doctor?' *J Pediatr Ophthalmol Strabismus* 1989; **26:** 55

21 Naumann GOH, Apple DJ *Pathology of the eye* New York: Springer, 1986 23–4

22 Mills PV, Hyper TJ, Duff GR Loop recessions of the recti muscles *Eye* 1987; **1:** 593–6.

23 Capó H, Repka MX, Guyton DL Hang-back lateral rectus recessions for exotropia *J Pediatr Ophthalmol Strabismus* 1989; **26:** 31–4

24 Schwartz RL, Koller HP Survey of sutures used in strabismus surgery *J Pediatr Ophthalmol Strabismus* 1981; **18:** 39–41

25 Bladyes JE The use of polyglactin-910 in muscle surgery *Ophthalmic Surg* 1975; **6:** 39–41

26 Goldstein JH, Prepas SB, Conrad SD. The effect of needle characteristics in strabismus surgery *Arch Ophthalmol* 1982, **100:** 617–8

27 Helveston EM *An atlas of strabismus surgery* 3rd ed St Louis. Mosby, 1985: 70–1

British Journal of Ophthalmology, 1990, 74, 494–495

MINI REVIEW

Neuro-ophthalmology

The most important neurone in the visual system is the second order neurone from the ganglion cell in the retina to the lateral geniculate body. Impairment of function is most likely to occur in the optic nerve. This review will therefore consider recent advances in knowledge in relation to the optic nerve. Three main aspects will be discussed – developmental, neuroradiological, and clinical advances.

DEVELOPMENT

One of the major challenges of the developmental neurobiologist is to understand what makes cells differentiate. The questions are beginning to be answered for neurones by some interesting work on the optic nerve.[1] The optic nerve is an excellent site to investigate because it contains no cell bodies and thus allows investigation of the neuronal supporting structure. Recent studies have shown that there are two types of astrocyte in the optic nerve, and these have been differentiated by morphology, antigenic phenotype, and response to growth factors. The astrocyte extends processes to the surface of the nerve, to the blood vessels forming a perivascular sheath, and to the nodes of Ranvier. Type I astrocytes are present before birth and send processes to blood vessels, whereas type II astrocytes occur in the second postnatal week and send processes to the nodes of Ranvier. The other glial cell in the optic nerve is the oligodendrocyte, which sends processes that concentrically wrap round the optic nerve to form an insulating myelin sheath.

Further investigation has shown that oligodendrocytes and type II astrocytes are derived from the same progenitor cell (0–2A progenitor cell). Evidence also suggests that platelet derived growth factor (PDGF) is secreted by type I astrocytes to stimulate 0–2A progenitor cells to proliferate. Similar studies in the retina have shown that retinal glial cells and Müller cells are derived from a similar cell line. Thus the scene is now set to investigate developmental abnormalities in the optic nerve (optic nerve glioma), optic disc anomalies (hypoplasia and drusen), and the retina (coloboma). We can therefore expect exciting advances in the next decade.

NEURORADIOLOGY

Assessment of the size of the optic nerve was virtually impossible 20 years ago, though information could occasionally be gained by the potentially hazardous procedures of injecting air into the orbit (orbital pneumography). The advent of the CT scan in the 1970s enabled clinicians for the first time to assess the optic nerve and the nerve sheath. The CT scan remains the investigation of choice for orbital diagnosis, and in particular for study of the optic nerve sheath.

ENLARGEMENT OF THE OPTIC NERVE AND SHEATH

Enlargement of the optic nerve sheath has been subdivided, depending on the CT appearances, into tubular, fusiform, and excrescent. Seventy-two cases of isolated optic nerve involvement were studied,[2] and the most common group was those with tubular enlargement. Common causes of tubular enlargement were papilloedema (10), compressive neuropathy (7), meningioma (7), neuritis (7), glioma, lymphoma, or leukaemia and perineural haematoma (4), and patulous subarachnoid space (5), with, less commonly, optic perineuritis and metastases. The only condition producing fusiform or excrescent enlargements were meningiomas and gliomas. It is interesting that the commonest cause of an enlarged nerve sheath is raised intracranial pressure, and when an enlarged sheath is seen with chronic disc swelling the differential diagnosis is between benign intracranial hypertension and an optic nerve sheath meningioma. Enlargement of the nerve sheath is a common accompaniment of sight threatening papilloedema and it supports the decision of a surgeon considering an optic nerve sheath decompression to go ahead.

The clinician having forsaken the skull *x* ray and the optic canal view in the 1970s for the greater information of CT scanning, now in the 1980s has to adapt again to new technology. Magnetic resonance imaging (MRI) uses the resonance of protons to provide images. Since water is the main component of living tissue, including the nervous system and the orbit, a proton image of the brain and orbit is primarily a water content picture. Protons lined up in a large magnetic field can be forced to precess* by a field of appropriate frequency applied at right angles. If the second field is turned off, the protons revert to their former position and the return is described by two time constants – one longitudinal (T_1) and the other horizontal (T_2). Excellent definition is obtained, and the images are free of bony artefact, since bone contains little water. Thus MRI has at the moment a technological superiority in the diagnosis of intrinsic disease of the optic nerve, chiasm, brain, cerebellum, and spinal cord, whereas CT scanning detects meningiomas and bone defects.

In multiple sclerosis, plaques of demyelination are seen because there is an increase in water content, initially due to oedema and later to gliosis. In cases of optic neuritis MRI scans show plaques elsewhere in the brain in 50–70% of cases, and plaques can also now be visualised in the optic nerve.[3] The MRI can be modified with a surface eye coil with coronal imaging of the optic nerve to produce the STIR sequence (short time inversion recovery).[4] Leber's hereditary optic neuropathy has also been studied by the STIR sequence.[5] Eight patients were studied, and in all cases the optic nerves showed an abnormal signal. In one case with monocular visual loss there was an abnormal signal in the affected optic nerve prior to involvement of the second eye. Thus MRI scanning has identified extensive involvement of the optic nerve in Leber's syndrome and hence provided a useful diagnostic role.

Further possible applications of MRI scanning include exploitation of drugs which traverse the bood-brain barrier (such as gadolinium), and its use for angiography and for metabolic mapping. At present CT reigns supreme for the detection of compressive and treatable lesions, whereas MRI scanning enables us to study intrinsic disease and has greater potential for future development.

---

*To precess to spin above a cone shaped axis, as in a wobbling spinning-top

CLINICAL FEATURES

It is surprising that so little headway has been made in understanding the pathogenesis or treatment of common conditions such as ischaemic papillopathy (anterior ischaemic optic neuropathy (AION)), optic neuritis, and nutritional amblyopia. Advances have, however, been made in some rare conditions, which I would therefore like to cover.

Leber's hereditary optic neuropathy

No devastation can be as great as the potential visual loss that occurs in this, the condition affecting young adults in their prime. Some interesting observations are furthering our knowledge about the subject.

Cardiac abnormalities. The high frequency of cardiac abnormalities (51% in one series[6] indicates that this may be a multisystem disease.[7] Cardiac abnormalities include the pre-excitation syndromes (the Wolff-Parkinson-White and the Lown-Ganong-Levine syndromes) which are associated with electrocardiographic abnormalities due to accessory A-V conduction tracts in the cardiac muscle, but are not usually symptomatic.

Enzymatic defects. Support for the cyanide toxicity theory has tended to falter over the past decade, but there does appear to be a deficiency of the enzyme thiosulphate sulphurtransferase (rhodanese) in these patients.[8] This enzyme is used in the detoxification of cyanide.

Pathogenesis. A mutation has recently been described on the subunit 4 gene of mitochondrial DNA; one aminoacid arginine is converted to histidine at codon 40.[9] As a result of the amino acid substitution a restriction enzyme binding site is lost. The mutation affects DNA energy production and cell respiration. In a further paper analysis of mitochondrial DNA[10] showed a mutation at base pair (bp) 11778, demonstrated by loss of a recognition site for the restriction enzyme endonuclease SfaNI. This mutation was accompanied by poor visual recovery, but patients without this mutation had regained useful vision. This therefore explains and will indeed predict the small number of patients (20%) with the potential for visual recovery. Further investigation may clarify the relationship of the microangiopathy to the disease, the incidence of visual loss, and the explanation for the greater incidence in males than females.

Optic neuropathy of sarcoidosis

Unexplained visual loss, often bilateral in association with enlargement of the optic nerve or nerve sheaths on CT scanning, may be attributed to granulomatous disease. Sarcoidosis is a multisystem disease in which non-caseating epithelioid cell granulomata occur in different sites. The optic nerves may rarely be affected without other clinical signs in the eye or in the nervous system. Visual loss may be acute or subacute and painful, or chronic and painless. Diagnosis was made by standard diagnostic criteria.[11] Cases are often steroid responsive, but, if high dosage is required, visual function may be retained by the use of azathioprine or chlorambucil.[12] In one recent case a man with progressive visual loss in one eye, with mild disc oedema and an expanded nerve on CT, was diagnosed as an optic nerve sheath meningioma. However, after several months a lesion on his forehead was biopsied and revealed sarcoidosis. Resolution of his visual symptoms with steroids leads me to reiterate the axiom that diagnosing the treatable is the most important part of the medicine.

M D SANDERS

St Thomas's Hospital,
London SE1 7EH

1 Raff MC Glial cell diversification in the rat optic nerve *Science* 1989, 243: 1450
2 Rothfus WE, Curtin HD, Slamovitz TL, Kennerdel JS Optic nerve/sheath enlargement. *Radiology, 1984*, 150: 409–15
3 Miller DH, Ormerod IEC, McDonald WI, *et al.* The early risk of MS after optic neuritis *J Neurol Neurosurg Psychiatry* 1988; 51: 1569–71
4 Johnson G, Miller DH, McManus D, *et al.* STIR sequences in MRI imaging of the optic nerve *Neuroradiology* 1987; 29: 238–45
5 Kermode AG, Moseley IF, Kendall BE, Miller DH, MacManus DG, McDonald WI Magnetic resonance imaging in Leber's optic neuropathy *J Neurol Neurosurg Psychiatry* 1989; 52: 671–4
6 Nickoskelainen E, Wanne O, Dahl M Pre-excitation syndrome and Leber's hereditary optic neuropathy *Lancet* 1985; i 696
7 Nikoskelainen EK, Sanontaus ML, Wanne OP, Katila MJ, Nummelin KU Leber's hereditary neuroretinopathy, a maternally inherited disease *Arch Ophthalmol* 1987, 105: 665–71.
8 Poole CJM, Kind PRN. Deficiency of thiosulphate transferase (rhodanese) in Leber's hereditary optic atrophy. *Br Med J* 1986, 292: 1229–30.
9 Wallace DC, Sing G, Loft MT, *et al.* Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy *Science* 1988; 242: 1427–30
10 Holt IJ, Miller DH, Harding AE. Genetic heterogenicity and mitochondrial DNA heteroplasty in Leber's hereditary optic neuropathy *J Med Genet* (in press)
11 Graham EG, Ellis CJK, Sanders MD, McDonald WI. Optic neuropathy in sarcoidosis. *J Neurol Neurosurg Psychiatry* 1986, 49. 756–63
12 Gelwan MJ, Kellen RI, Burde RM, Kupersmith MJ Sarcoidosis of the anterior visual pathway: successes and failures *J Neurol Neurosurg Psychiatry* 1988, 51: 1473

British Journal of Ophthalmology, 1990, 74, 496–497

CASE REPORTS

Hemifacial atrophy: an unusual cause of enophthalmos

K N Hakin, C Yokoyama, J E Wright

Abstract

We report on two cases of enophthalmos, caused by maxillary atrophy, a rarely reported monostotic forme fruste of hemifacial atrophy.

The commonest causes of enophthalmos are congenital orbital asymmetry, trauma, and malignancy.[1] A rare cause is hemifacial atrophy (Parry-Romberg disease), a disease characterised by progressive atrophy of the subcutaneous tissues and, less frequently, of muscle and bone, usually of one side of the face. We report two cases of enophthalmos caused by an unusual form of hemifacial atrophy, the atrophy localised to the maxilla alone, with no soft tissue involvement.

Case Reports

CASE 1

A 35-year-old woman presented with a one-year history of a 'sunken' right eye. The patient complained of an occasional retrobulbar ache on the right side, but was otherwise healthy, with no relevant medical or ocular history.

On examination there was a relative lowering of the right eyebrow, a deepened right superior sulcus and flattening of the right cheek (Fig 1). The visual acuities were 6/5 in either eye. The right eye was 4 mm enophthalmic and depressed 2 mm, but there was full range of ocular movements. Ocular examination and general examination, including a full neurological assessment, gave otherwise normal results.

Moorfields Eye Hospital, City Road, London EC1V 2PD
K N Hakin
C Yokoyama
J E Wright

Correspondence to:
Mr K N Hakin.

Accepted for publication 15 March 1990

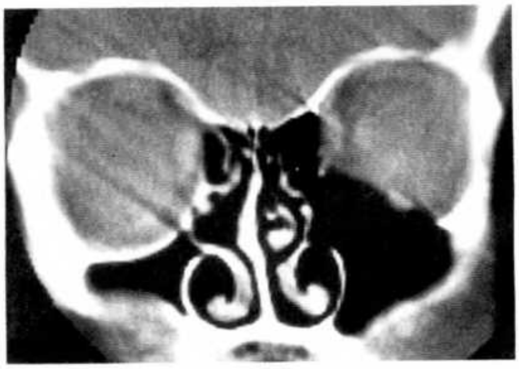


Figure 2: Case 1. CT scan demonstrating imploded right maxillary sinus.

A CT scan showed the right enophthalmos and a shrunken maxillary sinus with smooth concavity of the sinus walls towards the sinus cavity (Fig 2). The orbital floor was intact, with a convexity downwards towards the maxillary sinus. There was no evidence of an inflammatory or neoplastic process.

CASE 2

A 40-year-old woman presented with a six-month history of a 'sunken' left eye, associated with a mild discomfort on attempted movement of that eye. There was no history of head or ocular trauma, though the patient had received dental treatment to the left upper jaw approximately six months before noticing the problem. The right eye had been amblyopic from childhood.

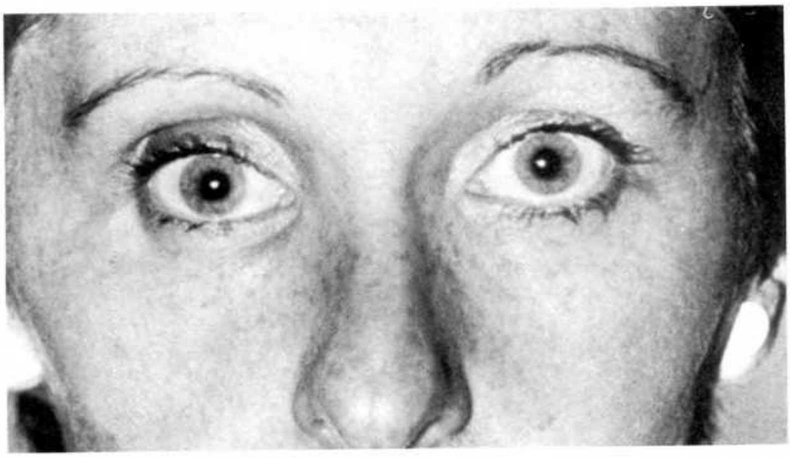


Figure 1: Case 1. Right enophthalmos.

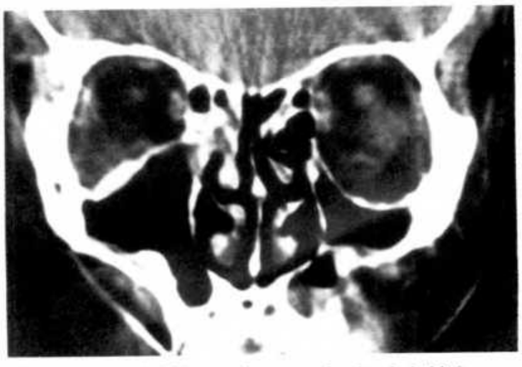


Figure 3: Case 2. CT scan demonstrating imploded left maxillary sinus.

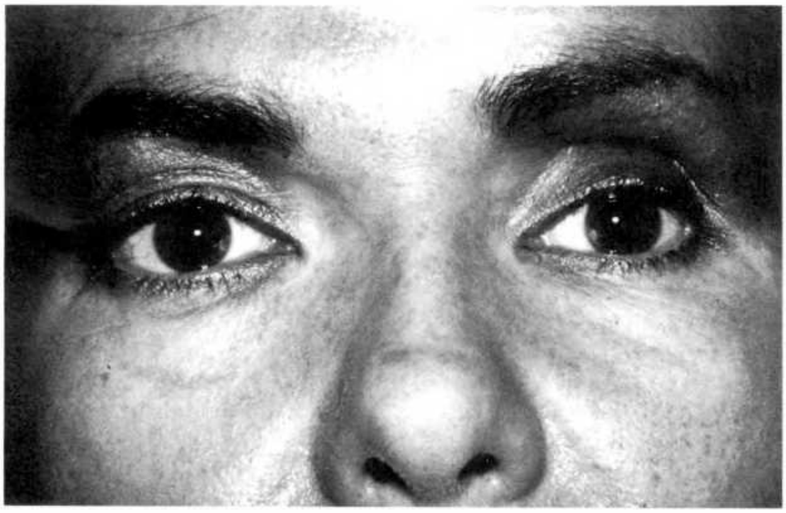


Figure 4: Case 2. Left enophthalmos.

The patient was initially referred to an ear, nose, and throat surgeon. Plain sinus *x* rays showed an opaque maxillary sinus suggesting possible sinusitis, but a sinus washout, and cytological examination and culture of the washings, gave normal results. A CT scan showed a shrunken maxillary sinus with slightly irregular bony contours, with no evidence of bony destruction (Fig 3).

The patient was referred for an ophthalmological opinion. Visual acuities were 6/18 in the amblyopic right eye and 6/6 in the left eye. There was mild tenderness over the left maxilla, with a deepening of the left superior sulcus (Fig 4). The left eye was 3 mm enophthalmic, but ocular movements were full. Ocular examination was otherwise normal.

To exclude a fungal sinusitis the left maxilla was re-explored through a Caldwell-Luc approach. The maxillary antrum was filled with altered blood and mucus from the washout six weeks previously. The orbital floor was intact, with a downward convexity into the antrum, and the antral walls were noted to be remarkably thin. The mucosa appeared normal. Histopathological examination of the antral contents showed mild chronic mucosal inflammation and blood clot, with no evidence of malignancy. Fungal culture of the contents was negative. A CT scan repeated three months later demonstrated a clear maxillary sinus but was otherwise unchanged.

Discussion

In a review of 26 cases Cline and Rootman reported the commonest causes of enophthalmos to be congenital asymmetry, trauma, and malignancy.[1] They stated that one or more of three mechanisms caused enophthalmos – structural abnormality, fat atrophy, and traction. Our cases were caused by implosion of the maxilla, a structural abnormality. This, however, was not congenital. There was no history of trauma, and radiological examination, with surgical exploration in the second case, excluded any sinus tumour or infection. In the absence of any other disease we considered our cases to be monostotic formes frustes of hemifacial atrophy (Parry-Romberg disease).

Hemifacial atrophy is a disease of unknown aetiology which usually begins in the first or second decade of life, initially with atrophy of fat and subcutaneous tissues of one side of the face. Atrophy of the muscle can follow, but bony involvement is said to be uncommon unless the onset is before the second decade.[2] An early sign may be a well demarcated furrow on the forehead, the coup de sabre, which marks the boundary between normal and atrophic tissue. There is involvement of the limbs and trunk in about 7% of cases,[3] and it may occasionally be bilateral.[4] It is thought that the condition may be caused by an abnormality in the sympathetic nervous system and that trauma to the affected area, including dental treatment, may be the trigger for the onset of the disease.[5,6] Our second case had received dental treatment six months prior to the onset of her symptoms.

Ocular involvement in hemifacial atrophy is well recognised and occurs in up to 40% of cases.[7] Pupil and lid anomalies, extraocular muscle imbalance, hypermetropia, and retinal pigmentary changes may be present,[2,6-11] but enophthalmos has been reported as the commonest ocular manifestation.[7] Ocular signs alone, however, are rare; they usually present as part of a spectrum of more extensive face and body changes. There have been two previous reports of hemifacial atrophy in which enophthalmos has been the only sign, occurring as a result of marked bony atrophy in the absence of any soft tissue change.[12,13]

Hemifacial atrophy should be remembered as a rare cause of acquired enophthalmos, but must always be considered a diagnosis of exclusion.

1 Cline RA, Rootman J. Enophthalmos: a clinical review. *Ophthalmology* 1984; **91**: 229–37.
2 Miller MT, Sloane H, Goldberg MF, Grisolano J, Frenkel M, Mafee MF. Progressive hemifacial atrophy (Parry-Romberg disease). *J Pediatr Ophthalmol Strabismus* 1987; **24**: 27–36.
3 Gorlin RJ, Pindborg JJ. *Syndromes of the head and neck*. 2nd ed. New York: McGraw-Hill, 1976: 341–3.
4 Hickman JW, Sheils WS. Progressive facial hemiatrophy. A report of a case with marked homolateral involvement. *Arch Intern Med* 1964; **113**: 716–20.
5 Kaufman MD. Masticatory spasm in facial hemiatrophy. *Ann Neurol* 1980; **7**: 585–7.
6 Johnson RV, Kennedy WR. Progressive facial hemiatrophy (Parry-Romberg syndrome). Contralateral extraocular muscle involvement. *Am J Ophthalmol* 1969; **67**: 561–4.
7 Muchnick RS, Aston SJ, Rees TD. Ocular manifestations and treatment of hemifacial atrophy. *Am J Ophthalmol* 1979; **88**: 889–97.
8 Smith B, Guberina C. Coloboma in progressive hemifacial atrophy. *Am J Ophthalmol* 1977; **84**: 85–9.
9 Aracena T, Roca FP, Barragan M. Progressive hemifacial atrophy (Parry-Romberg syndrome): report of two cases. *Ann Ophthalmol* 1979; **11**: 953–8.
10 Karney H, Baum JL. Refractive change as initial sign of progressive facial hemiatrophy. *Am J Ophthalmol* 1975; **79**: 878–9.
11 Sugar SH, Banks TL. Fuchs's heterochromic cyclitis associated with facial hemiatrophy (scleroderma en coup de sabre). *Am J Ophthalmol* 1964; **57**: 627–32.
12 Goldhammer Y, Kronenberg J, Tadmor R, Braham J, Leventon G. Progressive hemifacial atrophy (Parry-Romberg's disease), principally involving bone. *J Laryngol Otol* 1981; **95**: 643–7.
13 Zafarulla MYM. Progressive hemifacial atrophy: a case report. *Br J Ophthalmol* 1985; **69**: 545–7.

British Journal of Ophthalmology, 1990, **74**, 498

Vitreous haemorrhage as a complication of HELLP syndrome

Steven R Leff, David L Yarian, Leo Masciulli, Stuart N Green, Roy E Baldomero

Abstract

In the last trimester of an uncomplicated pregnancy a woman developed a spontaneous vitreous haemorrhage. She was later diagnosed as having HELLP syndrome, a recently described disorder comprising haemolytic anaemia, elevated liver enzymes, and a low platelet count in women with severe pre-eclampsia or eclampsia. We believe this rare complication of pregnancy to be the cause of the intraocular bleeding.

Complications during pregnancy often affect the eyes. Sometimes the eye symptoms precede other systemic changes necessary for a correct diagnosis, so that ophthalmologists must be cautious when diagnosing a disorder in a pregnant woman with any new ocular condition.

Case report

A 33-year-old woman, seven months pregnant, was referred for ophthalmic examination. She had noted a sudden decline in the vision in her left eye several days earlier, not associated with any systemic complaint or undue exertion. Her past medical history was negative. She was unaware of any complications in her pregnancy. On ocular examination the Snellen visual acuity was 20/30 right eye, 20/100 left. The intraocular pressures and anterior segment examinations were normal in both eyes. A fundus examination of the right eye showed it to be entirely normal. A fundus examination of the left eye revealed two globular preretinal haemorrhages, each several disc diameters in size, straddling the supratemporal arcade. A small amount of breakthrough vitreous haemorrhage obscured much of the detail of the posterior pole findings, though the retina was otherwise grossly intact and appeared normal. The patient's obstetrician was advised of the findings, although the cause of this condition was not clear. A follow-up obstetric examination and blood pressure determinations were reported as normal.

Over the next two weeks the vitreous haemorrhage gradually resolved, though there was still a preretinal haemorrhage in the superior fundus, presumably overlying the source of the inital bleed. Approximately one month after the initial ophthalmic examination the patient developed uncontrolled hypertension as a result of toxaemia and was referred to a tertiary care centre for further obstetric management. An emergency caesarean section was required. Laboratory work up at that time revealed a haemoglobin of 14·3 g/dl, a platelet count of 28×10^9/l, serum aspartate transaminase (SGOT) of 365 units, serum glutamic pyruvic transaminase (SGPT) of 222 units, and lactic dehydrogenase (LDH) of 1217 units. Although anaemia was not present, the remaining abnormal laboratory values supported a diagnosis of HELLP syndrome (haemolytic anaemia, elevated liver enzymes, and a low platelet count in women with severe pre-eclampsia or eclampsia).

The patient's metabolic parameters gradually returned to normal, and both mother and child did well. The patient returned for follow-up ophthalmic examination one month after delivery. The Snellen visual acuity in the left eye was then 20/30. Fundus examination of the left eye showed that nearly all the preretinal haemorrhage had become reabsorbed. A tiny fibrotic scar was noted over a small branch arteriole in the superior fundus, which was previously obscured by the overlying blood, and which probably represented the healed focus of the previous haemorrhage.

Discussion

Ocular changes associated with toxaemia complicating pregnancy have been described elsewhere.[1] In the HELLP syndrome,[2] observed in women with severe pre-eclampsia or eclampsia, severe hypertension is often only transient or entirely absent. We believe that our patient suffered from unrecognised thrombocytopenia secondary to HELLP syndrome at the time of her initial visual complaint. Although the retinal haemorrhage was probably a result of this clotting abnormality, an unrecognised transient episode of hypertension related to pre-eclampsia may have also contributed to the rupture of the susceptible site in a peripheral retinal vessel. To our knowledge this is the first description of a patient suffering an intraocular haemorrhage as a consequence of HELLP syndrome.

Retina-Vitreous Center, 77 Milltown Road, East Brunswick, NJ 08816, USA
S R Leff
D L Yarian
L Masciulli
S N Green

Department of Obstetrics and Gynecology, Newark Beth Israel Medical Center, Newark, NJ 07112, USA
R E Baldomero

Correspondence to:
Steven R Leff, MD.

Accepted for publication
22 March 1990

1 Sunness JS. The pregnant woman's eye. *Surv Ophthalmol* 1988; 32: 219–44.

2 Weinstein L. Syndrome of hemolysis, elevated liver enzymes and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol* 1982; 142: 159–63.

Calculate with confidence

CIA software

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton. The program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- non-parametric analyses

For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program may also be used in conjunction with the book *Statistics with Confidence,* which provides numerous worked examples. The software is available for IBM compatibles on either a $5\frac{1}{4}$″ or a $3\frac{1}{2}$″ disk.

Price: £65.00. Educational establishments, research institutes, and the NHS — £45.95. Prices include VAT in the UK and air mail despatch abroad.

The book *Statistics with Confidence – Confidence intervals and statistical guidelines* is available price £7.95 in the UK and £9.50 abroad (BMA members £7.45 and £9.00, respectively)

- -

RDER FORM BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE, England

Please send me .... copy/copies of *Confidence Interval Analysis (CIA)* at £65.00 (full price) or £45.95 (educational establishments, research institutes, and the NHS).

Size of disk required ☐ $5\frac{1}{4}$″ disk ☐ $3\frac{1}{2}$″ disk *(please tick relevant box)*

Please send me .... copy/copies of *Statistics with Confidence – Confidence intervals and statistical guidelines* at UK £7.95 and abroad £9.50 (BMA members £7.45 and £9.00 respectively)

I enclose .... *(please make cheques payable to* **British Medical Journal**) or debit my credit card

☐ American Express ☐ Mastercard ☐ Visa Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Card Expiry Date .... Signature ....

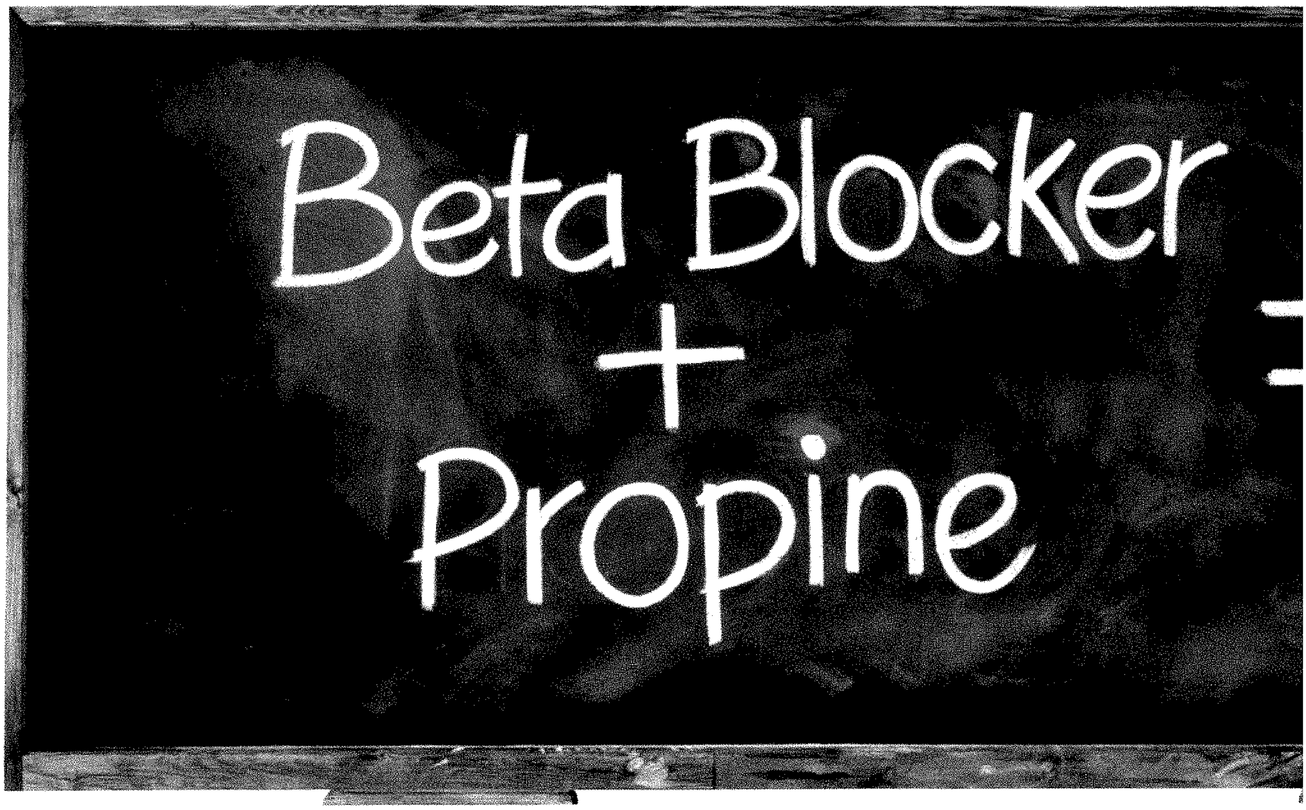
BMA Membership No. (where applicable) ....

NAME (BLOCK LETTERS PLEASE) ....

ADDRESS ....

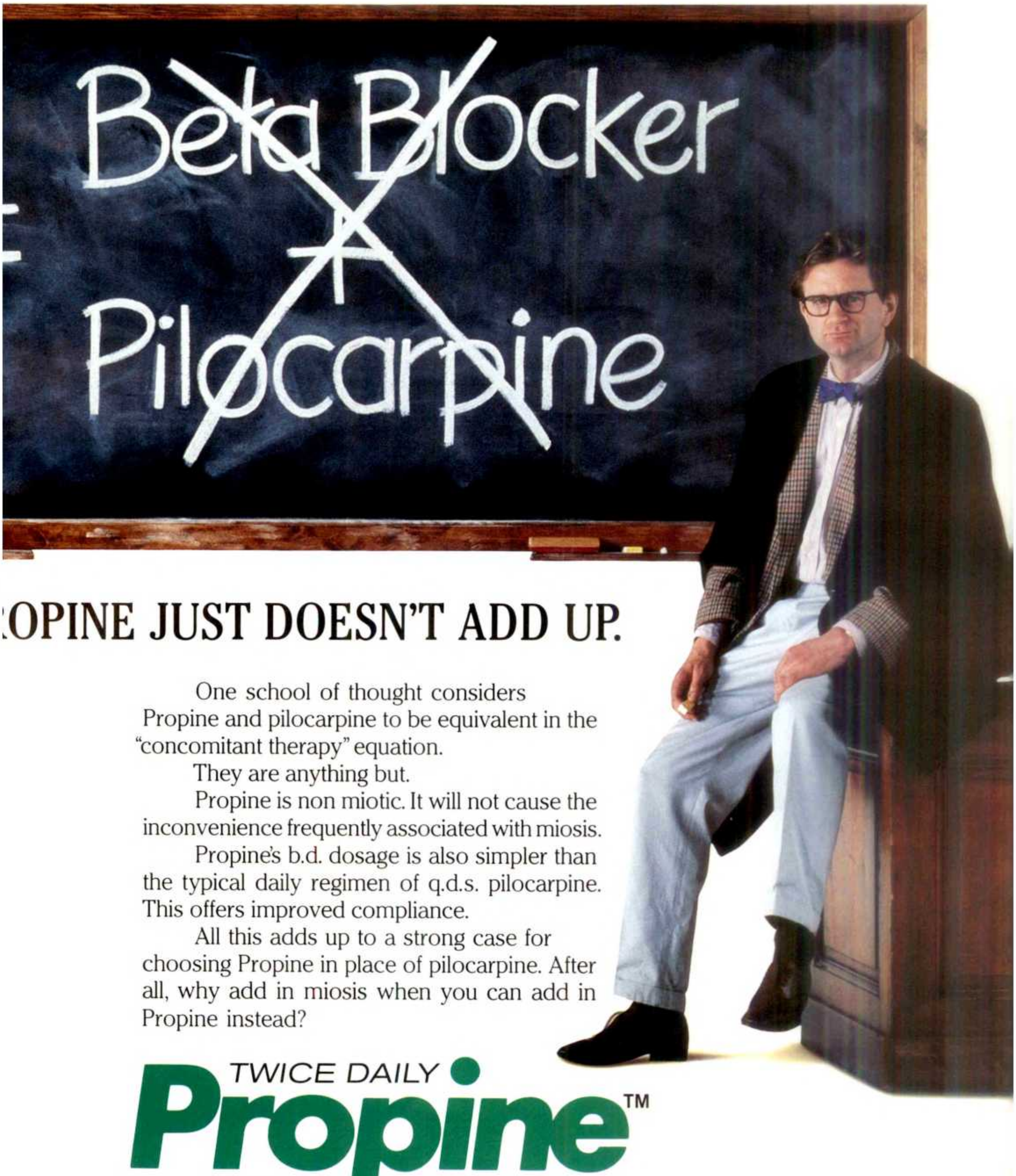
....

.... POSTAL CODE ....



EQUATING PILOCARPINE WIT

PROPINE™ Prescribing Information
Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be
with caution in patients with narrow angles since dilation of the pupil may trig
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adre
use in aphakic patients. Prompt reversal generally follows discontinuance of the
Macular oedema with dipivefrin does present as a possibility in the aphakic patien
product contains benzalkonium chloride and should not be used by patients cont
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachy
arrhythmias and hypertension have been reported with ocular administrat



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY ●
Propine™
dipivefrin hydrochloride

A CLEAR CHOICE IN THE GLAUCOMA EQUATION

aline, and may occur rarely with Propine therapy. Ocular: the most frequently ed side-effects are conjunctival injection, and burning and stinging on instillation. nd vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis, een reported occasionally. Adrenochrome deposits in the conjunctiva and cornea een associated rarely with use of dipivefrin. Follicular conjunctivitis has been ed during long term therapy with Propine. The condition is reversible upon discon- ce of the drug. **Pharmaceutical precautions** Store at room temperature. Discard used contents 28 days after opening the bottle. **Legal category** POM. **Package quantities** Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990.

TM denotes trademark

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.

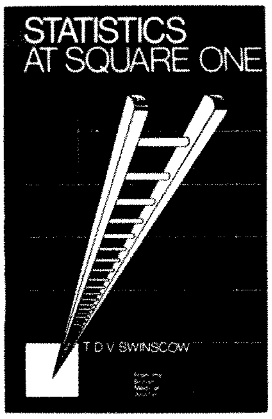
STATISTICS WITH CONFIDENCE
— Confidence intervals and statistical guidelines
MARTIN J GARDNER
DOUGLAS G ALTMAN
STATISTICS WITH CONFIDENCE
BMJ

Many medical journals, including the *British Medical Journal*, now expect scientific papers submitted to them to contain confidence intervals when appropriate. Why? what are they? and how do you calculate them? *Statistics with Confidence* tells you. A clear explanation of the reasons for using confidence intervals is followed by detailed presentation of methods of calculation, including numerous worked examples and specially compiled tables. To make things even easier, a computer programme, Confidence Interval Analysis (CIA), for calculating confidence intervals, has been specially designed by Martin Gardner and details are available from the Publishing Department, *British Medical Journal.*

Price: Inland £7.95;
Abroad £9.50
BMA members: Inland £7.45;
Abroad: £9.00

Eighth edition

The statistical testing of data is indispensable in many types of medical investigation and a help on countless occasions in clinical practice. This book provides step by step instruction. Subjects covered include standard deviation, χ^2 tests, t tests, non-parametric tests, and correlation. The book includes sections on Fisher's exact probability test and rank correlation not published in the original *BMJ* series. Methods specially adapted to pocket calculators.

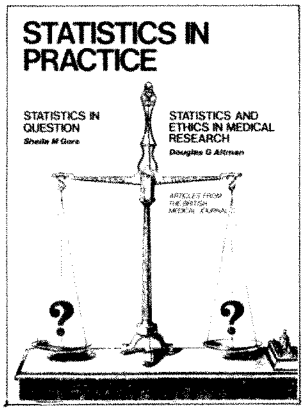


Price: Inland £3.00;
Abroad £4.50
BMA members: Inland £2.50;
Abroad: £4.00

"He uses statistics as a drunken man uses lamp-posts — for support rather than illumination." *

Let the *BMJ* throw light on your methods and help your results stand up

* *Andrew Lang*


STATISTICS IN PRACTICE
STATISTICS IN QUESTION
Sheila M Gore
STATISTICS AND ETHICS IN MEDICAL RESEARCH
Douglas G Altman
ARTICLES FROM THE BRITISH MEDICAL JOURNAL
?
?

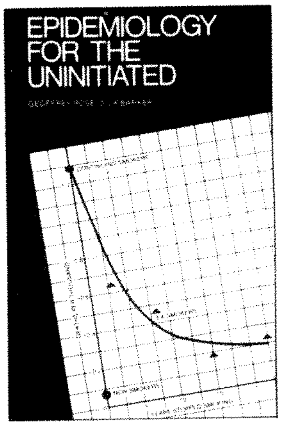
Fourth impression

No doctor can afford to ignore statistics: most modern medical research uses statistics. This important and authoritative book provides clear information on designing studies, applying statistical techniques, and interpreting studies that use statistics. It can be easily understood by those with no statistical training and should be read by all those who want to keep abreast of new developments.

Price: Inland £8.95;
Abroad £11.00
BMA members: Inland £7.45;
Abroad: £10.00

Second edition

Epidemiology has its own techniques of data collection and interpretation and its necessary jargon of technical terms, and in *Epidemiology for the Uninitiated* Professors Geoffrey Rose and David Barker guide the novice expertly through the theory and practical pitfalls. The second edition of this popular *BMJ* handbook has been revised to include further details of epidemiological methods and some of their more dramatic applications, such as the investigations on the Spanish cooking oil epidemic, and AIDS.



Price: Inland £3.95;
Abroad £5.50
BMA members: Inland £3.45;
Abroad: £5.00

ORDER FORM

BRITISH MEDICAL JOURNAL, P.O. Box 295,
London WC1H 9TE, England *or any leading medical bookseller*

Please send me
☐ Statistics with Confidence
☐ Statistics at Square One
☐ Statistics in Practice
☐ Epidemiology for the Uninitiated
All prices include postage, by air abroad

NAME ....

ADDRESS ....

....

POSTCODE ....

I enclose .... BMA Membership No. ....

Please make cheques payable to **British Medical Journa**
debit my credit card (please tick box)

☐ Access/Mastercard ☐ Barclaycard/Visa
☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

CARD EXPIRY DATE ....

SIGNATURE ....

☐ Please send me a book catalogue

British Journal of Ophthalmology, 1990, **74**, 499–501

Optic nerve avulsion due to forced rotation of the globe by a snooker cue

P G Hykin, I D Gardner, S M Wheatcroft

Abstract

We report a case of partial avulsion of the optic nerve caused by sudden rotation of the globe due to a snooker cue injury. Minimal direct ocular trauma occurred. This case supports the belief that sudden rotation of the globe is the major mechanism of optic nerve avulsion. We include the first results of ultrasound examination that demonstrate optic nerve injury in such a case and believe that, in conjunction with fluorescein angiography and computerised tomography, it is important in the full evaluation of such cases.

Optic nerve avulsion is an uncommon injury that has been reported following major head trauma[1] and, less frequently, after pointed but blunt non-penetrating orbital injuries with minimal ocular trauma.[2] The method of avulsion in the latter group is thought to result from either sudden rapid rotation of the globe,[3] or a sudden rise in intraocular pressure forcing the optic nerve posteriorly along its sheath,[4] or by the object causing anterior displacement of the globe as it enters the orbit, avulsing the nerve from the eye.[4] If total avulsion of the nerve occurs, the eye is completely blind. Varying degrees of visual loss and altitudinal field defects may follow partial avulsions.[5] Investigation of these cases has been by clinical evaluation, fluorescein angiography, and computerised tomography.[6] Ultrasound has previously been unhelpful in demonstrating actual optic nerve damage.[7] There is no effective treatment.

Case report

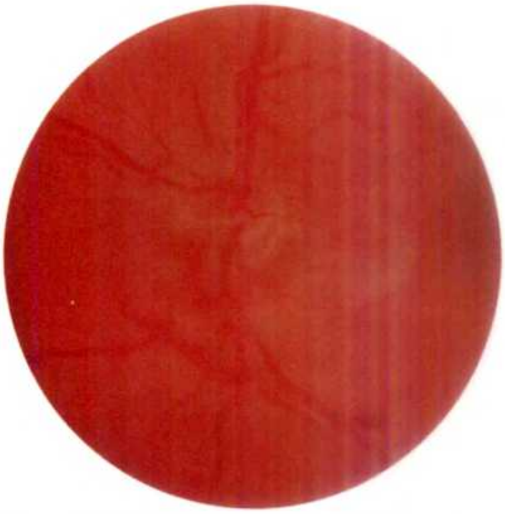


Figure 1 Left inferotemporal optic nerve avulsion with hold-up of axoplasmic flow in the corresponding retina. Vitreous haemorrhage is present.

A 22-year-old man presented with sudden loss of vision in the left eye. He had been balancing a snooker cue, tip downward on the palm of his hand, immediately above his face. He recalled it slipping and hitting his left eye and was immediately aware of loss of his left upper visual field. There was no previous history of ocular disease.

On examination the left visual acuity was counting fingers, and no Ishihara colour plates were seen. There was a left afferent pupillary defect. There was a small corneal abrasion at the limbus in the 12 o'clock position and a 1 cm horizontal tear of the bulbar conjunctiva approximately 5 mm superior to this. Occasional red blood cells were seen in the anterior chamber. The intraocular pressure was 16 mmHg. There were mild vitreous and peripapillary haemorrhages. At least the inferotemporal portion of the optic nerve was avulsed, with hold up of axoplasmic flow in the corresponding retina thought to be secondary to direct avulsion of nerve fibres,

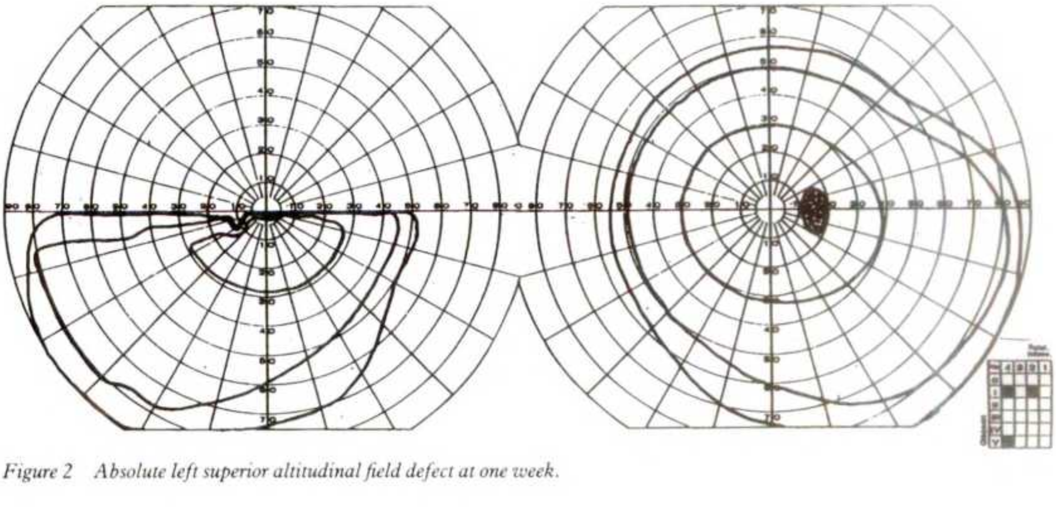


Figure 2 Absolute left superior altitudinal field defect at one week.

Department of Ophthalmology, Oxford Eye Hospital, Oxford
P G Hykin
I D Gardner
S M Wheatcroft

Correspondence to:
Mr P G Hykin, FRCS, Oxford Eye Hospital, Walton Street, Oxford OX2 6AN.

Accepted for publication
8 March 1990

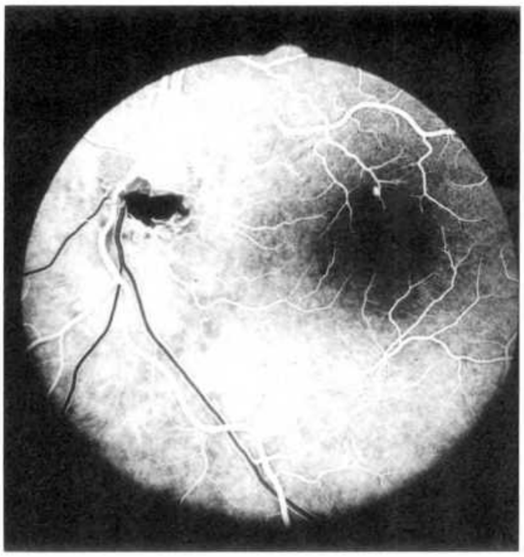


Figure 3 Fluorescein angiogram showing simultaneous appearance of the late venous phase in the superior half of the retina with the early venous phase inferiorly. There is complete non-perfusion of the lower half of the optic disc.

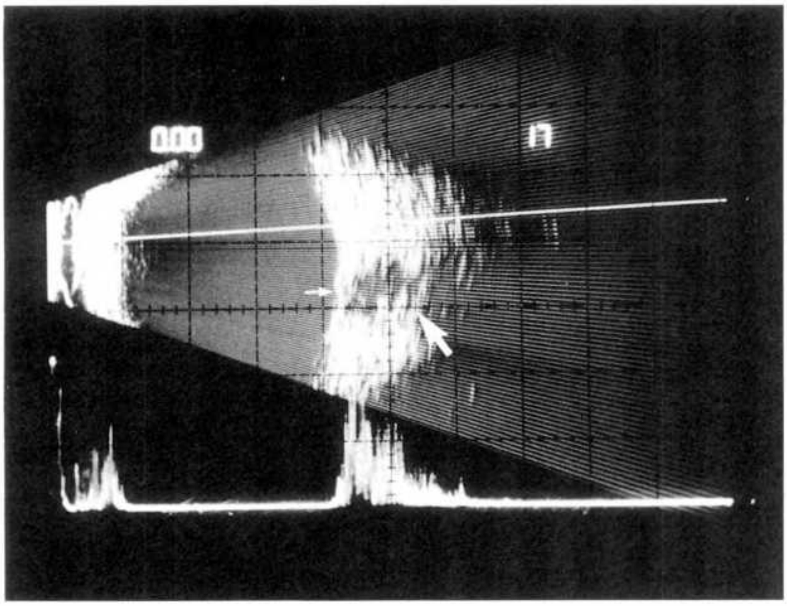


Figure 4

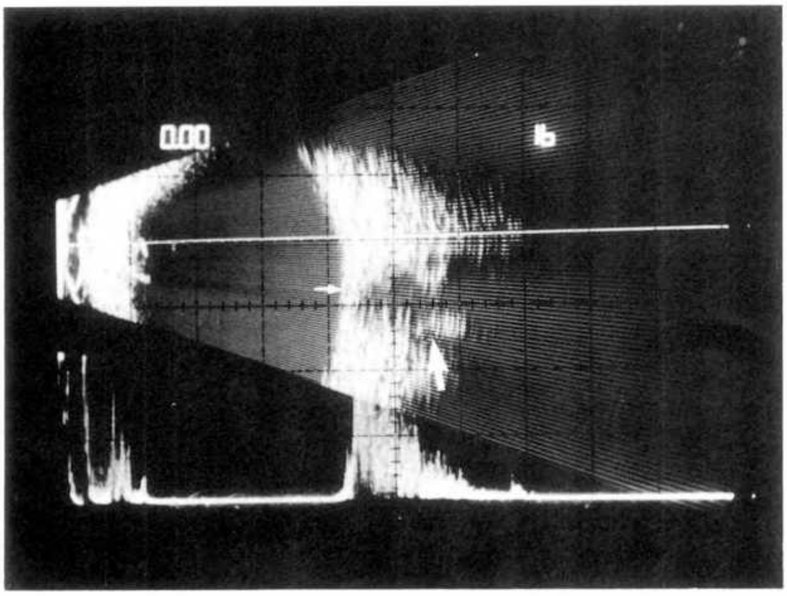


Figure 5

Figures 4 and 5 Vertical (Fig 4) and horizontal (Fig 5) B-scan ultrasonography. There is optic nervehead signal attenuation (small arrows) but increased signal arising from the anterior third of the optic nerve (large arrows).

which we believe to be previously unreported. Optic disc oedema was present superiorly (Fig 1). A left superior altitudinal field defect to confrontation was present and was confirmed on formal perimetry some days later, after the vitreous haemorrhage had cleared (Fig 2). The right eye was normal.

Fluorescein angiography at six weeks showed delayed filling of the inferior retinal circulation as evidenced by the simultaneous appearance of the late venous phase in the superior half of the retina with the early venous phase inferiorly. In addition there was complete non-perfusion of the lower half of the optic disc, with mild late fluorescein leakage superiorly due to residual disc oedema (Fig 3).

At the same time, an ultrasound B scan demonstrated loss of signal attenuation at the optic disc (Figs 4, 5, small arrow), confirming the clinical picture of partial optic nerve avulsion. Posterior to this the ultrasound showed greater signal attenuation than normal, indicative of ingrowth of glial scar tissue into the damaged optic nerve (Figs 4, 5, large arrow). Forty-eight hours after injury the left visual acuity had improved to 6/9. At six weeks the acuity was 6/9, and the superior altitudinal field defect remained. Avulsion and pallor of the inferior half of the optic nerve head were clearly visible. Full thickness retinal striae, seen temporal to the optic disc, were thought to represent the retinal response to compressive injury (Fig 6).

Discussion

This patient presented with an avulsion of the inferior half of the left optic nerve. It seems likely that the injury was caused by the tip of the snooker cue forcefully rotating the globe superiorly, as evidenced by the site of impact. This resulted in the optic nerve being violently rotated downwards and forwards. In this position maximum stress would have been conveyed to the inferior fibres within the optic nervehead, leading to their avulsion from the globe. This agrees with the previously held view that damage to optic nerve fibres occurs in the leading edge of the nerve in the direction of globe rotation.[3]

Several other mechanisms have been proposed to account for optic nerve avulsion in similar cases. A sudden rise in intraocular pressure with resultant posterior displacement of the nerve within its sheath has been suggested.[4] Marked damage to the optic nerve, however, in the absence of significant intraocular damage, seems unlikely. It has also been suggested that if a pointed instrument penetrates the orbit the globe may be momentarily displaced forwards, causing avulsion of the optic nerve. This again seems unlikely, as one would predict accompanying damage to the extraocular muscles in such a situation, which is not a consistent finding.[4]

The results of fluorescein angiography have been described in only a few cases of optic nerve avulsion and have been normal,[8] showed an absence of the retinal circulation,[4] or showed delayed venous filling.[9] Vascular shunts have been described between the peripapillary choroidal and retinal circulations.[10] Our case had

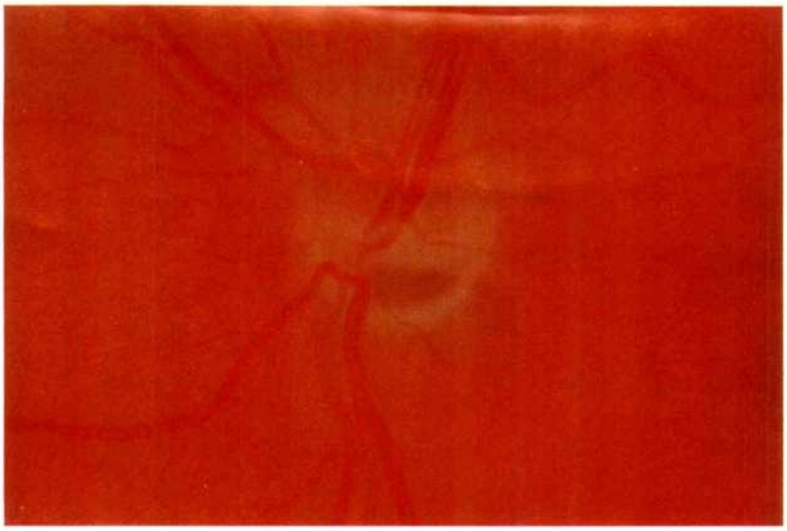


Figure 6 The left optic disc at six weeks demonstrating avulsion and pallor of the inferior half of the optic nerve, full thickness retinal striae temporal to the disc and inferior retinal vascular attenuation. Mild residual vitreous haemorrhage remains.

delayed filling of the circulation to the lower half of the retina and, as reported once before,[11] complete absence of capillary filling to the inferior half of the optic disc. This suggests compromise of the inferior retinal circulation and occlusion of the blood supply to the lower half of the optic nervehead. This could well be explained by the stripping off of the recurrent pial branches of the paraoptic short posterior ciliary arteries which lead on to form the circle of Zinn-Haller.[12] We believe this vascular damage to have occurred at the time of injury and to explain the immediate sudden onset of the superior altitudinal field defect. This vascular insufficiency was still present at six weeks (Fig 3).

The findings on B-scan ultrasonography of an attenuated optic nervehead signal and additional echoes arising from within the optic nerve, suggesting the ingrowth of glial scar tissue,[13] have not been previously reported in optic nerve avulsion,[5] though orbital haemorrhage has been demonstrated by ultrasonography in a few cases.[7] We do not believe these optic nerve changes are specific to this condition but suggest that B-scan ultrasonography is an important part of the full investigation of such cases, especially if, as is frequently the case, vitreous haemorrhage obscures the optic disc.

We thank Professor A J Bron for permission to report this case, and Mr P Parker for photographic assistance.

1 Nau HE, Gerhard L, Foerster M, *et al*. Optic nerve trauma: clinical, electrophysiological and histological remarks. *Acta Neurochir Wien* 1987; **89**: 16–27.
2 Chow AY, Goldberg MF, Frenkel M. Evulsion of the optic nerve in association with basketball injuries. *Ann Ophthalmol* 1984; **16**: 35–7.
3 Williams DF, Williams GA, Abrams GW, *et al*. Evulsion of the retina associated with optic nerve avulsion. *Am J Ophthalmol* 1987; **104**: 5–9.
4 Sanborn GE, Gonder JR, Goldberg RE, Benson WE. Evulsion of the optic nerve: a clinicophathological study. *Can J Ophthalmol* 1984; **19**: 10–6.
5 Rosenberg PN, Stasior OB. Optic nerve evulsion and transection. *Adv Ophthalmic Plast Reconstruct Surg* 1987; **6**: 63–9.
6 Chang M, Eifrig DE. Optic nerve avulsion. *Arch Ophthalmol* 1987; **105**: 322–3.
7 Coleman DJ, Lizzi L, Lack RL. *Ultrasonography of the eye and orbit*. Philadelphia: Lea and Febiger, 1977: 345.
8 Park JH, Frenkel M, Dobbie JG, Choromokos E, *et al*. Evulsion of the optic nerve. *Am J Ophthalmol* 1971; **72**: 969–71.
9 Hart JCD, Pilley SFJ. Partial evulsion of the optic nerve: fluorescein angiographic study. *Br J Ophthalmol* 1970; **54**: 781–5.
10 Archer DB, Canavan YM. Contusional injuries of the distal optic nerve. *Trans Ophthalmol Soc NZ* 1983; **35**: 14–23.
11 Zinn KM, Kirban EH. Partial avulsion of the optic nervehead secondary to local trauma. *Mt Sinai J Med* (NY) 1989; **51**: 629–32.
12 Olver JM, Spalton DJ, McCartney ACE. Microvascular study of the retrolaminer optic nerve in man. *Eye* 1990; **4**: 7–24.
13 Skalka HW, Kline LB. Comparative value of ultrasound and CT scanning in orbital optic nerve evaluation. In: Herkes HE, ed. Ophthalmic ultrasonography proceedings of 9th SIDUO Congress. *Doc Ophthalmol Proc Ser* 1982; **38**: 365–6.

British Journal of Ophthalmology, 1990, **74**, 502–504

Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis

C Mark Antle, Karim F Damji, Valerie A White, Jack Rootman

Abstract

A case of uveal malignant melanoma and contralateral optic nerve glioma is described in a 53-year-old Caucasian male with multiple uveal melanocytic hamartomas and neurofibromatosis. The eye was enucleated, and histologically the melanoma was found to consist of 70% epithelioid cells, with many bizarre, multinucleated forms. CT scan demonstrated a non-enhancing, fusiform enlargement of the contralateral optic nerve with enlargement of the optic canal and intracranial extension. This combination of tumours has not previously been reported in a patient with neurofibromatosis and serves to emphasise the common neuroectodermal origin of tumours in this autosomal dominant condition.

Optic nerve glioma[1,2] and uveal malignant melanoma[3-13] have both been reported in von Recklinghausen's neurofibromatosis (NF). While the incidence of optic nerve glioma varies from 10 to 70%,[2] only 11 cases of uveal malignant melanoma in NF are reported.[3-13] In NF uveal malignant melanoma has been reported with acoustic schwannoma[3] and with orbital neuroma.[5] We describe the previously unreported association of uveal malignant melanoma and contralateral optic nerve glioma in a patient with multiple uveal melanocytic hamartomas and neurofibromatosis.

Case report

A 53-year-old Caucasian man with multiple cutaneous neurofibromata, café-au-lait spots, and a family history of NF presented with a four-day history of spots and blurring in the left eye rapidly progressing to total grey-out of vision.

The visual acuities were 20/20–3 in the right eye and 20/400 in the left, with a left afferent pupillary defect. The interpalpebral fissures, results of exophthalmometry, and IOP measurements were normal and symmetrical. Neither globe showed displacement. Multiple Lisch nodules and iris naevi were seen, particularly in the left eye, which also had a large inferior sentinal vessel and a cataract. There was a large ciliochoroidal tumour between 4 and 8 o'clock, with 9–10 mm of elevation, a total retinal detachment, and anterior iris displacement between 4 and 6 o'clock.

Ultrasonography showed a solid, horseshoe shaped mass in the choroid extending from inferotemporal to inferonasal quadrants.

Computed tomography showed a normal left orbit and a left globe of normal size with an enhancing lobulated uveal mass in its inferior half extending bilaterally to the ora (Fig 1) without extrascleral extension. On the right the optic nerve had a non enhancing, fusiform enlargement, with expansion of the optic canal and intracranial extension. No cerebellopontine angle or internal auditory canal abnormality was seen.

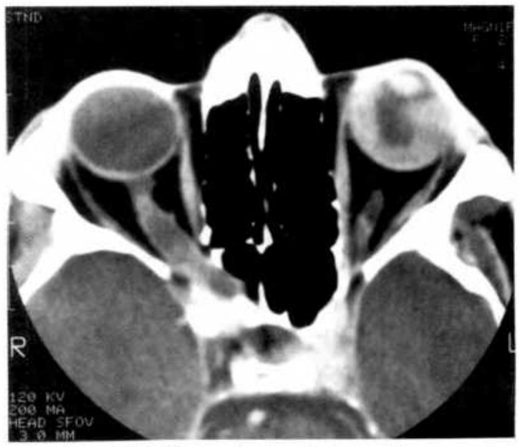


Figure 1   Axial CT scan showing fusiform enlargement of the optic nerve with intracranial extension (right) and lobulated uveal mass (left).

Malignant melanoma was suspected, and it was confirmed on intraoperative fine needle aspiration biopsy, which showed numerous malignant epithelioid melanocytes with large vesicular nuclei and prominent nucleoli. The biopsy was followed by a cryoenucleation. The globe was 24–25 mm in diameter with corneal measurements of 13×11·5 mm. Oblique sectioning exposed a black tumour with a 17 mm base and a height of 7 mm. The overlying retina was detached.

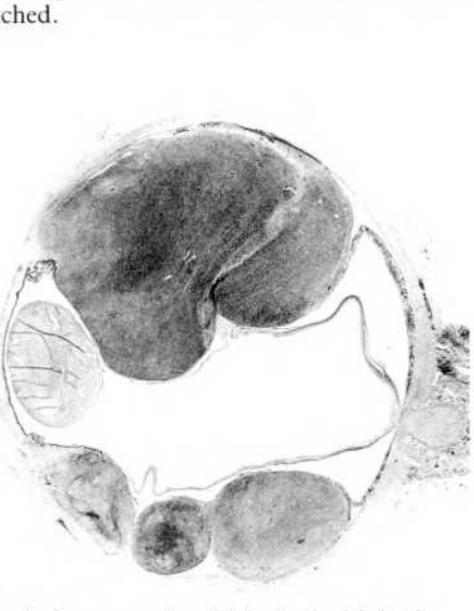


Figure 2   Low power view of globe showing lobulated tumour arising from the uveal tract and associated retinal detachment. (Haematoxylin and eosin, ×2·7.)

Vancouver General Hospital and University of British Columbia, Vancouver, British Columbia, Canada
Department of Pathology
C M Antle
K F Damji
V A White
J Rootman

Department of Ophthalmology
V A White
J Rootman

Correspondence to:
Dr J Rootman, Eye Care Centre, 2550 Willow Street, Vancouver, British Columbia, Canada V5Z 3N9.

Accepted for publication
8 March 1990

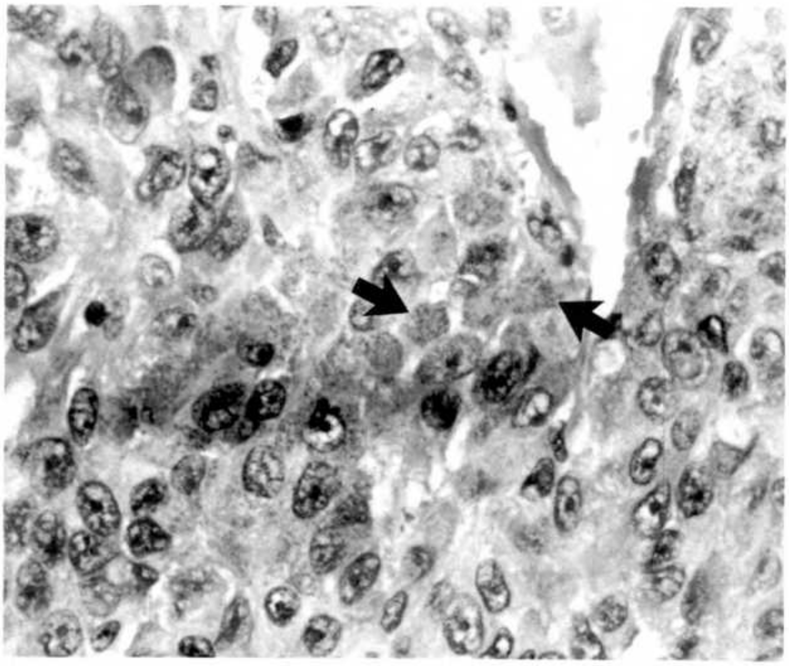


Figure 3 Uveal malignant melanoma with epithelioid cells showing granular cytoplasmic S100 positivity (arrows). (Bleached preparation; immunoperoxidase staining for S100 antigen; ×800.)

Histologically a poorly differentiated malignant melanoma arose from the uvea, abutted the lens, occupied the pars plana, and extended three-quarters of the way to the posterior pole (Fig 2). The densely pigmented tumour cells were 70% epithelioid and 30% spindle, with many bizarre, multinucleated forms (Fig 3). The tumour stained moderately for S100 protein and strongly with the monoclonal antibody HMB45. Large sinusoidal spaces and focal areas of haemorrhage and necrosis were identified. There was no paraemissarial extension. The detached retina was degenerated.

In the neovascularised iris spindle to polygonal shaped cells, many with intranuclear inclusions, formed numerous S100-positive melanocytic hamartomas (Fig 4). In the choroid multiple diffuse hamartomatous aggregations of melanocytes, some extending round the emissaria posteriorly, were present and stained strongly positive for S100 protein and occasionally with HMB45 (Fig 5).

The patient presented three months later with diffuse metastatic disease and died 13 months after enucleation.

Discussion

Neurofibromatosis, first described by von Recklinghausen in 1882,[14] is a common autosomal dominant disorder with a prevalence of 1 in 3000.[15 16] It has one of the highest mutation rates in humans.[17] Though it was previously considered to be a heterogeneous disorder with variable expression, linkage analysis in NF families has recently identified a consistent mutation at a single locus on chromosome17.[18]

Melanocytic and glial lesions of NF are derived from the neural crest. The association of optic nerve glioma and NF is established,[1 2] and an increased incidence of uveal malignant melanoma is also noted[19] despite the small number of cases (11) reported.[3-13] Uveal naevi are also found more frequently.[11 15] Concurrent malignant melanoma and optic nerve glioma have not previously been reported, but the conjunction illustrates the pathogenesis of NF as a 'complex neurocristopathy' as initially defined by Bolande.[20] This concept envisages NF as a defect in development and regulation in which tissues derived from the neural crest show an increased incidence of benign tumours such as neurofibromas, schwannomas, neuromas, gliomas, meningiomas, café-au-lait spots, other cutaneous naevi, uveal naevi,[1 2 16 21-23] and malignant tumours such as malignant schwannoma,[24 25] pheochromocytoma,[26 27] cutaneous malignant melanoma,[24 28-30] and uveal malignant melanoma.[3-13] A predisposition to uveal malignant melanoma may also exist because of the increased incidence of choroidal naevi in NF[31] and the supposition that malignant melanoma arises from these naevi.[32]

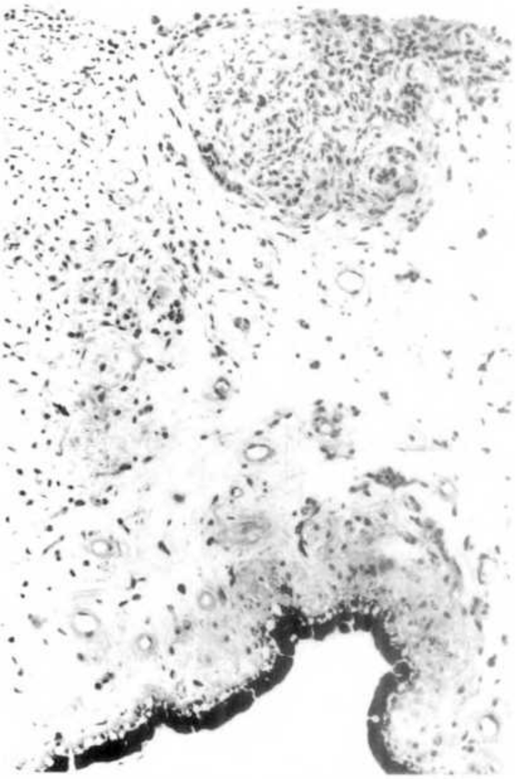


Figure 4 Melanocytic hamartoma of the iris. (Haemotoxylin and eosin, ×80.)

Other features of NF cannot be attributed directly to maldeveloped neural crest but may arise secondarily to interactions with other developing tissues, leading to additional anomalies[15] such as malignant tumours (rhabdomyosarcoma, nephroblastoma, and myelogenous leukaemia),[33-37] mesodermal defects (macrocephaly, pseudoarthrosis, kyphoscoliosis, short stature, sphenoid wing dysplasia), diminished intellect, speech defects, and pruritus.[16]

The commonest ocular feature of NF is the Lisch nodule, present in over 90% of adult patients.[22 23] Additional neural crest derived ocular features include neurofibromas of eyelid, conjunctiva, and orbit, café-au-lait spots, prominent corneal nerves, uveal naevi, choroidal glial hamartomas, optic nerve gliomas, intraocular schwannomas, sphenoid wing dysplasia,[17 22 23 38] and uveal malignant melanoma.[3-13]

The average age of patients with NF-related

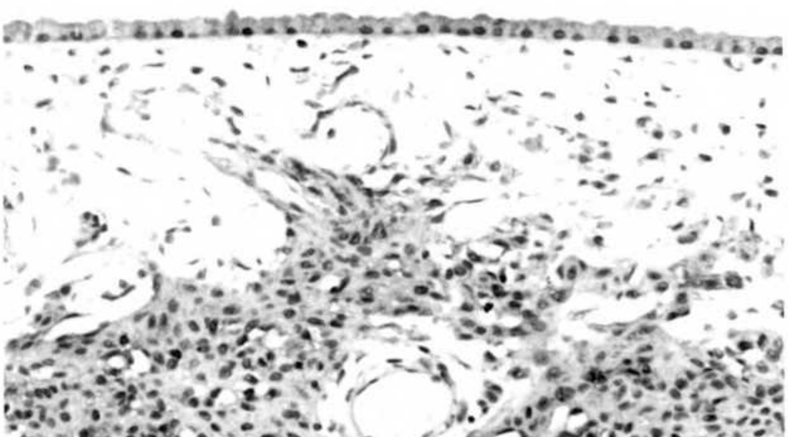


Figure 5 Melanocytic hamartoma of the choroid. (Immunoperoxidase staining for S100 antigen, ×160.)

uveal malignant melanomas is reported as 47, and our patient was 55. Two-thirds of enucleations for uveal malignant melanoma in the general population occur after age 50.[39] Despite the lack of sex predilection in NF alone, nine of the 11 previously reported patients in whom it was associated with uveal malignant melanoma were female, a distribution not seen in other series of uveal malignant melanoma. Seven tumours were reported as spindle cell, three as mixed cell, and one as epithelioid cell. The tumour in our case was mixed. Four cases showed extrascleral extension at enucleation, while the present case did not. The malignant cell type of our tumour and the large size suggested a poor outcome, with a five-year survival less than 40%.[40]

1 Rush JA, Younge BR, Campbell RJ, MacCarthy CS. Optic glioma. Long term follow-up of 85 histopathologically verified cases. *Ophthalmology* 1982; **89:** 1213–9.

2 Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford RP. von Recklinghousen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology* 1984; **91:** 929–35.

3 Bair HL, Love JG. Acoustic neurofibroma associated with melanoepithelioma of the choroid: successful removal of both tumors. *Mayo Clin Proc* 1937; **12:** 481–5.

4 Gartner S. Malignant melanoma of the choroid and von Recklinghausen's disease. *Am J Ophthalmol* 1940; **23:** 73–8.

5 Strachov VP. Recklinghausen's disease, neurinoma of the right orbit and neoplasm of the left choroid. *Vestn Oftalmol* 1941; **18:** 12–16 (in Russian).

6 Szekler R. Ein Uvealsarkom bei einem Mitglied einer Familie mit Recklinghausenscher Krankheit. *Ophthalmologica* 1954: **126:** 248–51.

7 Nordmann J. Cancer de la choroide et maladie de Recklinghausen. *Bull Soc Ophtalmol Fr* 1961; **5:** 322–5.

8 Nordmann J, Brini A, Ruolt J. Temeur melanique de la choroide et neurinomes chez un même sujet. *Bull Soc Ophtalmol Fr* 1963; 7: 551–3.

9 Yanoff M, Zimmerman LE. Histogenesis of malignant melanomas of the uvea: III. The relationship of congenital ocular melanocytosis and neurofibromatosis to uveal melanomas. *Arch Ophthalmol* 1967; **77:** 331–6.

10 Cernea P, Dobrescu G. Mélanome malin uvéal, manifestation de la maladie de Recklinghausen. *Ophthalmologica* 1973; **166:** 161–71.

11 Wiznia RA, Freedman JK, Mancini AD, Shields JA. Malignant melanoma of the choroid in neurofibromatosis. *Am J Ophthalmol* 1978; **86:** 864–87.

12 Croxatto JO, Charles DE, Malbran ES. Neurofibromatosis associated with nevus of Ota and choroidal melanoma. *Am J Ophthalmol* 1981; **92:** 578–80.

13 Specht CS, Smith TW. Uveal malignant melanoma and von Recklinghausen's neurofibromatosis. *Cancer* 1988; 62: 812–7.

14 Crump T. Translation of case reports in Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen bei F.v. Recklinghausen. *Adv Neurol* 1981; **29:** 259–76.

15. To KW, Rabinowitz SM, Friedman AH, Merker C, Cavanaugh CP. Neurofibromatosis and neural crest neoplasms: primary acquired melanosis and malignant melanoma of the choroid. *Surv Ophthalmol* 1989; **33:** 373–9.

16 Riccardi VM. von Recklinghausen neurofibromatosis. *N Engl J Med* 1981; **305:** 1617–27.

17 Sergeyev AS. On the mutation rate of neurofibromatosis. *Hum Genet* 1975; **28:** 129–38.

18 Barker D, Wright E, Nguyen K, *et al.* Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 1987; **236:** 1100–2.

19 Font RL, Ferry AP. The phakomatoses. *Int Ophthalmol Clin* 1972; **12:** 31–42.

20 Bolande RP. The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. *Hum Pathol* 1974; 5: 409–29.

21 Huson S, Jones D, Beck L. Ophthalmic manifestations of neurofibromatosis. *Br J Ophthalmol* 1987; **71:** 235–8.

22 Lewis RA, Riccardi VM. von Recklinghausen neurofibromatosis. Incidence of iris hamartoma. *Ophthalmology* 1981; **88:** 348–54.

23 Ilgren EB, Kinnier-Wilson LM, Stiller CA. Gliomas in neurofibromatosis: a series of 89 cases with evidence for enhanced malignancy in associated cerebellar astrocytomas. *Pathol Annu* 1985; **1:** 331–58.

24 Brasfield RD, Das Gupta TK. von Recklinghausen's disease: a clinico-pathologic study. *Ann Surg* 1972; **175:** 86–104.

25 Sayed AK, Bernhardt B, Perez-Atayde AR, *et al.* Malignant schwannoma in siblings with neurofibromatosis. *Cancer* 1987; **59:** 829–35.

26 Healy FH, Mekelatos CJ. Pheochromocytoma and neurofibromatosis. *N Engl J Med* 1958; **258:** 540–3.

27 Modlin IM, Farndon JR, Shephard A, *et al.* Pheochromocytoma in 72 patients: clinical and diagnostic feature, treatment and long term results. *Br J Surg* 1979; **66:** 456–65.

28 Riccardi VM, Eichner JE. *Neurofibromatosis: phenotype, natural history and pathogenesis.* Baltimore: Johns Hopkins University Press, 1986: 162–8.

29 Silverman JF, Blahove M, Collins JL, Norris HT. Cutaneous malignant melanoma in a black patient with neurofibromatosis. *Am J Dermatopathol* 1988; **10:** 536–40.

30 Mastrangelo MJ, Goepp CE, Patel YA, Clark WH. Cutaneous melanoma in a patient with neurofibromatosis. *Arch Dermatol* 1979; **115:** 864–5.

31 Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. *Adv Neurol* 1981; **29:** 33–56.

32 Yanoff M, Zimmerman, LE. Histogenesis of malignant melanoma of the uvea. *Arch Ophthalmol* 1967; **77:** 331–6.

33 Bader JL, Miller RW. Neurofibromatosis and childhood leukemia. *J Pediatr* 1978; **92:** 925–9.

34 Bestak M, Miller DR, Mouradian JS. Juvenile chronic myelogenous leukemia and dermal histiocytosis. *Am J Dis Child* 1979; **133:** 831–3.

35 McKeen EA, Bodurtha J, Meadows AT, *et al.* Rhabdomyosarcoma complicating multiple neurofibromatosis. *J Pediatr* 1978; **93:** 992–3.

36 Stay EJ, Vawter G. The relationship between nephroblastoma and neurofibromatosis. *Cancer* 1977; **39:** 2550–5.

37 Walden PAM, Johnson AG, Bagshawe KD. Wilms's tumour and neurofibromatosis. *Br Med J* 1977; i: 813.

38 Freedman SF, Elner VM, Donev ID, Gunta G. Albert DM. Intraocular neurilemmoma arising from the posterior ciliary nerve in neurofibromatosis. *Ophthalmology* 1988; **95:** 1559–64.

39 Zimmerman LE. Malignant melanoma of the uvea. In: Spencer WH, ed. *Ophthalmic pathology.* Philadelphia: Saunders, 1986: 2072–136.

40 McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type and enucleation as risk factors in metastasis. *Hum Pathol* 1982; **13:** 123–32.

British Journal of Ophthalmology, 1990, **74**, 505–508

Aneurysmal bone cyst of the sphenoid with orbital involvement

Jill V Hunter, Cheryl Yokoyama, Ivan F Moseley, John E Wright

Moorfields Eye Hospital, City Road, London, Department of Radiology
J V Hunter
I F Moseley

Orbital Clinic
C Yokoyama
J E Wright

Correspondence to:
Dr Jill V Hunter, Lysholm Department of Radiology, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG.

Accepted for publication
15 February 1990

Abstract

We present a case of aneurysmal bone cyst involving the roof of the orbit and sphenoid bone, with plain film, computed tomography, and magnetic resonance imaging findings. The natural history and treatment depend on the presence of associated abnormalities such as fibrous dysplasia or a giant cell tumour. In this case the lesion was solitary and was successfully removed, so that possible complications from radiotherapy were avoided.

Aneurysmal bone cyst (ABC) is uncommon. The commonest site in 40–50% of cases is the metaphysis of a long bone. In the skull ABC is rare, representing less than 1% of cases: of 59 in the literature 15 involved the orbit[1-15] of which four affected the sphenoid bone[1 8 12 14] and one the sphenoid sinus.[10]

There is an association between peripheral ABC and other bony abnormalities; an associated lesion has implications for the choice of treatment. We describe a boy with a lone ABC involving the greater and lesser wings of the sphenoid.

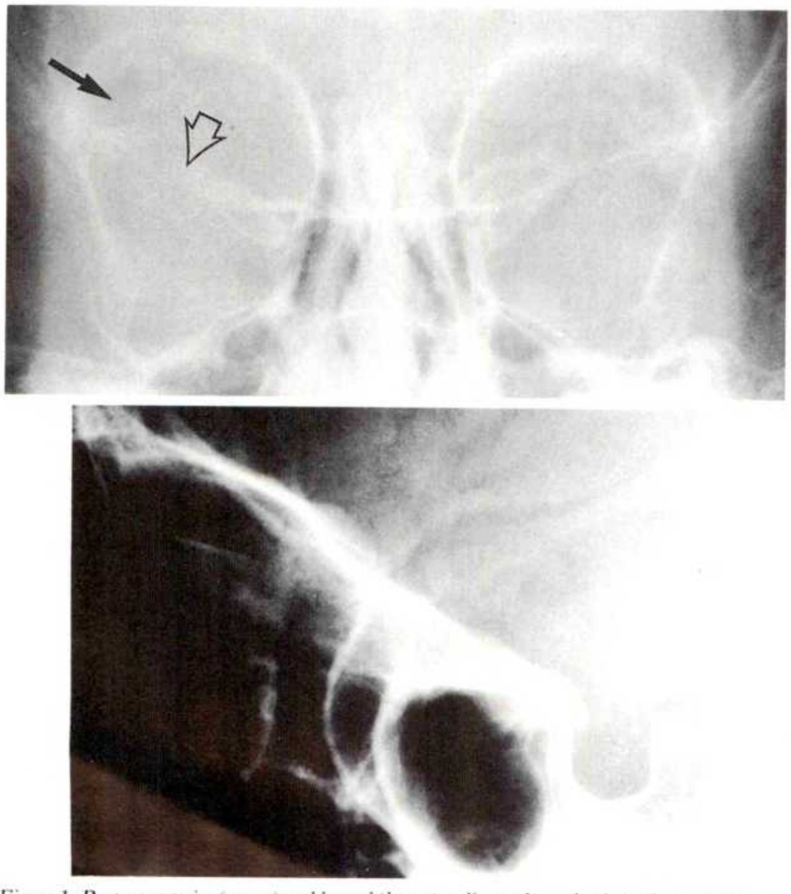


Figure 1: Postero-anterior (upper) and lateral (lower) radiographs at the time of presentation (November 1988). The right orbit is marginally larger than the left, and there is a small area of osteolysis with surrounding sclerosis (solid arrow) in its roof. The sphenoid ridge is slightly less distinct (open arrow) than its fellow.

Case report

A 7-year-old white boy presented with a history of one month's variable, painless, periorbital swelling, without visual disturbance. There was no relevant past history, in particular no head injury. There was right sided periorbital swelling, with 4 mm axial proptosis. Visual acuity was 6/9 in both eyes; examination otherwise gave normal results. Plain skull radiographs showed a small mixed density lesion posteriorly in the roof of the orbit (Fig 1). Six days later there was no palpable mass or sign of inflammation. The right eye still showed 3 mm axial proptosis, unchanged with head positioning or the valsalva manoeuvre. The physical findings were thought to represent a small orbital haemorrhage.

The findings on examination remained unchanged despite further episodes of intermittent proptosis and lid swelling. Fourteen weeks later, however, the right eye was displaced 6 mm forwards, with limitation of upgaze; horizontal movement was less affected (Fig. 2). Retinal striae were noted, though the optic disc appeared normal. Visual acuity was now 6/12 in the right eye. There was no afferent pupillary defect.

X-ray computed tomography (CT) (Fig. 3) demonstrated a very large destructive lesion in the sphenoid bone with layering of high density material suggestive of a cavity containing blood.

Biopsy was performed via a lateral canthotomy (Mr J E Wright). A bluish-purple mass, displacing the periosteum away from the bone towards the orbit, was incised and a cavity containing old blood was entered. Deep to this lay highly vascular, friable tissue, biopsy revealed multinucleate giant cells and osteoid consistent with ABC.

Magnetic resonance imaging (MRI) (Fig 4) showed a large, rounded, well defined mass apparently extending from the right sphenoid into the orbit. T_1-weighted (IR 1500/500/40)

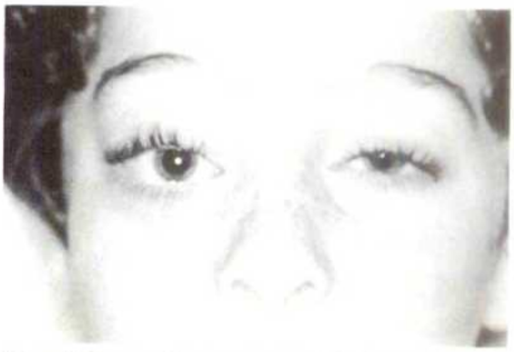


Figure 2: Preoperative appearances with right proptosis.

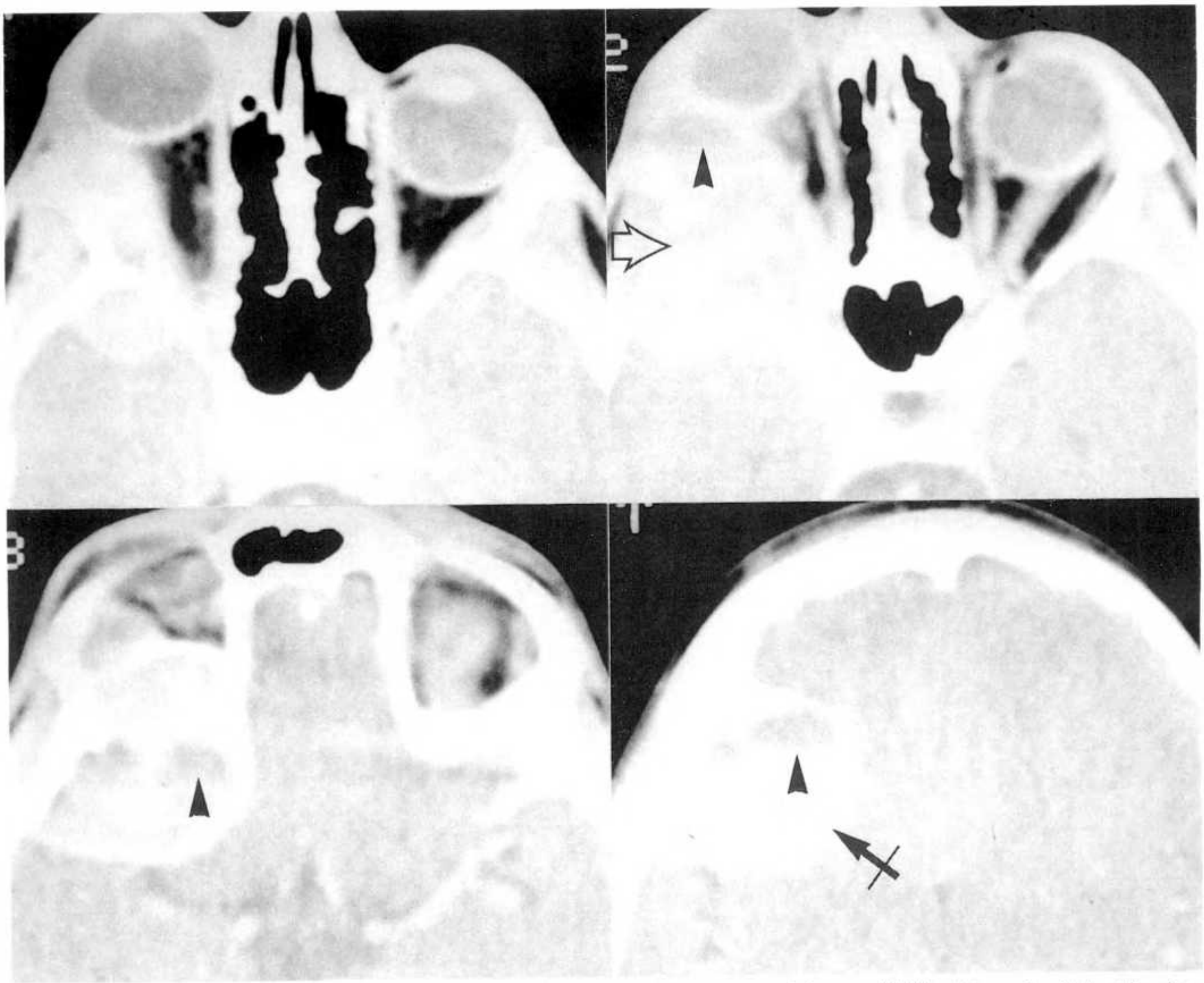


Figure 3: Computed tomography with intravenous contrast medium (February 1989). A large mass containing several fluid levels (arrow heads) due to layering of blood expands into the orbit and the anterior and middle cranial fossae, eroding the bone laterally (open arrow) towards the temporal fossa. It appears to have a capsule (crossed arrow).

images indicated the presence of clotted blood.

At frontal craniotomy (Professor D N Harrison) a large, vascular, mass was found occupying the orbital roof from 1 cm behind the orbital rim to the middle cranial fossa. Most of the roof and the posterosuperior wall of the orbit was absent. The mass adhered to the optic nerve posteriorly. It was separated from the frontal lobe and orbital periosteum and removed piecemeal. The cavity was curetted and right

TABLE I *Clinical features of orbital ABC*

Reference number	*Age (years)*	*Sex*	*Site*	*Side*	*Proptosis*	*Diplopia*	*Visual acuity*	*History (months)*	*Trauma*	*Pain*	*Treatment*	*FU*
1	22	M	Roof sph.	R	Yes	Yes	Normal	8 years*	No	No	Surgery	2
2	31	M	Roof	L	Yes	No	Normal	3	No	No	Surgery	NA
3	8	M	Medial	R	Yes	NA	NA	2	No	No	Surgery	0·5
4	14	F	Roof	L	No	No	NA	1	No	HA	Surgery	5
5	8	F	Roof	R	Yes	No	Normal	8 Days	No	No	Surgery	0·5
6	10	F	Roof	R	Yes	Yes	Normal	3	No	No	Surgery	NA
7	26	F	Medial	R	Yes	Yes	NA	NA	No	No	Surgery	NA
8	16	F	Lat sph.	L	Yes	Yes	Normal	5	No	No	Surgery	3
9	1·2	M	Roof	L	Yes	NA	NA	<1	No	No	Surgery ×2	NA
10	10	M	Sph. Sinus	L+R	No	No	Reduced	Recent	No	No	Surgery ×2	6
11	11	F	Roof	L	Yes	NA	NA	6	No	No	RT+surgery	0·75
12	1·3	M	Roof sph.	L	Yes	?Yes	Normal	3	No	No	RT+surgery ×2	12
13	12	F	Roof	R	Yes	No	Reduced	10 Days	No	No	Surgery ×3	3
14	19	F	Lat. sph.	L	Yes	Yes	Normal	NA	No	Yes	Surgery	1·5
15	42	F	Roof	L	Yes	Yes	Normal	2	No	Yes	Surgery	1·5
Hunter *et al*	7	M	Roof sph.	R	Yes	No	Reduced	2 weeks	No	No	Surgery	0·75

M=male. F=female. L=left. R=right. sph.=sphenoid. lat.=lateral. NA=not available. RT=radiotherapy. HA=headache. FU=follow-up. *Rapid progression over one year.

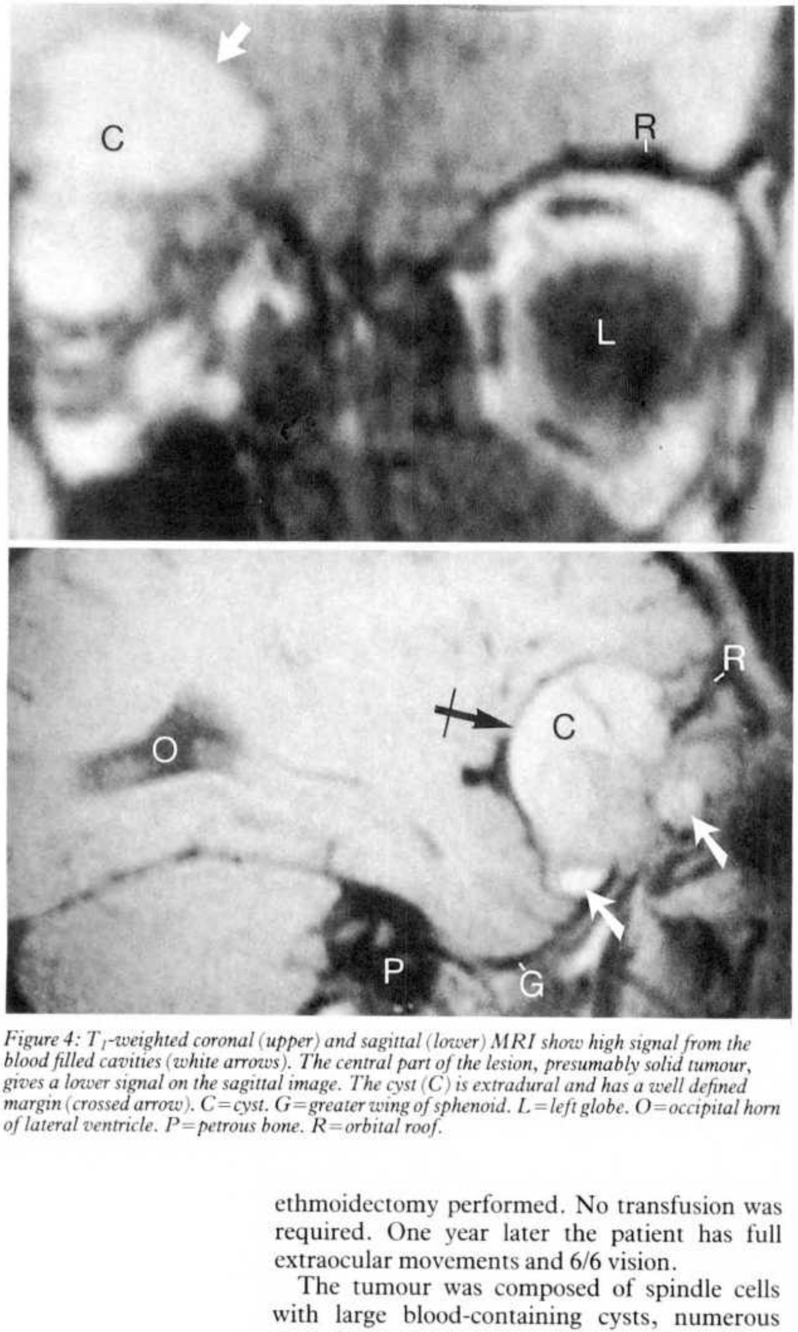


Figure 4: T_1-weighted coronal (upper) and sagittal (lower) MRI show high signal from the blood filled cavities (white arrows). The central part of the lesion, presumably solid tumour, gives a lower signal on the sagittal image. The cyst (C) is extradural and has a well defined margin (crossed arrow). C=cyst. G=greater wing of sphenoid. L=left globe. O=occipital horn of lateral ventricle. P=petrous bone. R=orbital roof.

ethmoidectomy performed. No transfusion was required. One year later the patient has full extraocular movements and 6/6 vision.

The tumour was composed of spindle cells with large blood-containing cysts, numerous osteoclast giant cells, and reactive bone, confirming the diagnosis of ABC (Bone Tumour Panel, Royal National Orthopaedic Hospital Stanmore).

TABLE II *Radiological features of orbital ABC*

Reference number	*Plain films*	*NM*	*Angiogram*	*CT (bone destruction)*	*Enhancement*	*MRI*
1	*+ve*					
2	*+ve*		*M*			
3	*+ve*					
4	*−ve*		*M*			
5	*−ve*					
6	*+ve*		*M*			
7	*+ve*		*M and B*			
8	*+ve*	*+ve*	*M*			
9	*+ve*		*M and B*			
10	*+ve*		*M and B*	*+ve*	*+ve*	
11	*+ve*					
12	*+ve*		*M*			
13	*+ve*		*M*			
14	*−ve*		*M*	*+ve*	*+ve*	
15	*+ve*			*+ve*		
Hunter *et al*	*+ve*			*+ve*		*+ve*

M=mass. B=blush. NM=nuclear medicine.

Discussion

Aneurysmal bone cyst[16] is a benign, multicystic, vascular lesion of young people. Up to 85% of cases occur before 20 years of age,[17] with one documented case in a 72-year-old.[18] There is a slight female preponderance.[17] Half of ABCs involve the metaphyses of long bones and one-fifth the spine. The skull and orbit are affected in about 1%; of 59 cases reported in the skull 15 involved the orbit.

Other bony lesions are present in up to one-third of cases. In 57 extracranial ABCs the most common associated lesions were: solitary bone cyst (18), osteoclastoma (14), and osteosarcoma (12).[18] Other associations include fibrous dysplasia, non-ossifying fibroma, chondroblastoma, fibromyxoma, and giant cell reparative granuloma.[19] At presentation ABC may be large, with a history of insidious onset of pain (in more than half) and swelling (in one-quarter). Pathological fracture may occur in the long bones or spine. Symptoms have typically been present for less than three months, though 6% of patients do not present for one year or more.[19] The recurrence rate for extracranial ABCs is 21–44%, higher rates occur with incomplete excision and in children.[17]

In the orbit ABC has been reported in nine females and six males aged from 14 months to 42 years. One case had bilateral orbital involvement from a sphenoid sinus ABC. Presenting symptoms included painless proptosis, diplopia, ptosis, headache, visual deterioration, and nasal congestion. The average duration of symptoms was two months (Table I and Table II).

Aneurysmal bone cyst may arise in the roof and/or walls of the orbit. One proposed cause is trauma, but in none of the orbital tumours was injury noted.

Sudden proptosis secondary to rapid expansion of the lesion – presumably haemorrhagic – is common. The rapidity of progression between the slightly abnormal plain film and the grossly pathological CT only 14 weeks later was striking and raised the possibility or malignancy, as in other cases.[13] However, Dabska and Buraczewski[20] described four radiological phases: osteolysis; rapid growth; stabilisation; and healing, with progressive ossification. The short history suggests that many patients present during the phase of rapid growth. As in our case, signs of globe compression such as retinal striae may be seen.

None of the reported orbital cases was secondary to another lesion. In keeping with the benign nature of ABCs, all remained extradural.

Accepted methods of treating peripheral ABCs include excision, curettage (sometimes with bone grafting), cryotherapy, and radiotherapy. Some of these are not applicable to the orbit. Review of the literature reveals two cases of orbital recurrence, following needling and partial excision, within two years. Two patients received radiotherapy after surgery.[11 12] One orbital ABC, mistaken for a giant cell tumour and treated with high-dose radiation, presented again as a heavily calcified mass.[12] No cases of osteogenic sarcoma complicating radiotherapy have been reported in the orbit, though this has occurred with extracranial ABCs.[20] Our patient remains well one year after operation.

CONCLUSION

Orbital aneurysmal bone cysts appear to form a well defined subgroup of ABC of the skull. Although rare, these potentially curable, benign lesions should be considered in young patients with painless proptosis of rapid onset.

1 Siedenbiedel H Brauner tumor der orbita *Klin Monatsbl Augenheilkd* 1953; 122: 86–90

2 Arnould G, Lepoire J, Tridon P, Schmitt J, Guerci O Exophtalmie unilaterale par kyste solitaire de l'orbite. *Rev Otoneuroophtalmol* 1961; 33; 59–61

3 Kubicz S, Sobieszczanska-Radoszewska L Przypadek tetniakowatej torbieli kostnej kosci sitowej i czolowej u chlopca 8 – letniego. *Otolaryngol Pol* 1962; 16: 665–9.

4 Costantini FE, Iraci G, Benedetti A, Melanotte PL. Aneurysmal bone cyst an intracranial space-occupying lesion: case report *J Neurosurg* 1966, 25: 205–7

5 Fite JD, Schwartz JE, Calhoun FP. Aneurysmal bone cyst of the orbit. *Ophthalmology* 1968; 72. 614–8

6 Offret G, Clay C, Lecoq P-J, Arrata M Kyste aneurysmal des os à localisation orbitaire *Bull Soc Ophtalmol Fr* 1971, 71: 1049–54.

7 Komorn RM. Management of vascular tumors of the head and neck. *South Med J* 1972; 65: 1106–12

8 Powell JQ, Glaser JS. Aneurysmal bone cyst of the orbit *Arch Ophthalmol* 1975; 93: 340–2

9 O'Gorman AM, Kirkham TH. Aneurysmal bone cyst of the orbit with unusual angiographic features. *A J R* 1976, 126: 896–9

10 Yee RD, Cogan DC, Thorp TR, Schut L. Optic nerve compression due to aneurysmal bone cyst. *Arch Ophthalmol* 1977; 954: 2176–9.

11 Flament J, Forest P, Boukoffa OS, Lankar A. Kyste osseux aneurismal de l'orbite. *J Fr Ophtalmol* 1979, 22· 131–4

12 Iraci G, Giordano R, Fiore D, Pizzi G, Tomazzoli-Gerosa L, Gerosa M. Exophthalmos from aneurysmal bone cyst of the orbital roof *Childs Nerv Syst* 1980; 6: 206–17.

13 Ronner HJ, Jones IS Aneurysmal bone cyst of the orbit: a review. *Ann Ophthalmol* 1983; 15: 626–9

14 Calliauw L, Roels H, Caemaert J Aneurysmal bone cysts in the cranial vault and base of skull. *Surg Neurol* 1985; 23: 193–8.

15 Johnson TE, Bergin DJ, McCord CD Aneurysmal bone cyst of the orbit *Ophthalmology* 1988; 95: 86–9

16 Jaffe HL, Lichtenstein L Solitary unicameral bone cyst with emphasis on the roentgen picture, the pathologic appearance, and the pathogenesis. *Arch Surg* 1942; 44: 1004–25.

17 Ruiter DJ, van Rijssel TG, van der Velde EA. Aneurysmal bone cysts *Cancer* 1977; 39: 2231–9

18 Levy WM, Miller AS, Bonakdarpour A, Aegerter E Aneurysmal bone cyst secondary to other osseous lesions *Am J Clin Pathol* 1975; 63: 1–8.

19 Biesecker JL, Marcove RC, Huvos AG, Mike V. Aneurysmal bone cysts. *Cancer* 1970; 26: 615–25

20 Dabska M, Buraczewski J. Aneurysmal bone cyst. *Cancer* 1969; 23: 371–89

British Journal of Ophthalmology, 1990, **74**, 509–510

Yellow forelock – a new neuro-ophthalmological sign

R I Kellen, B Schrank, R M Burde

Abstract

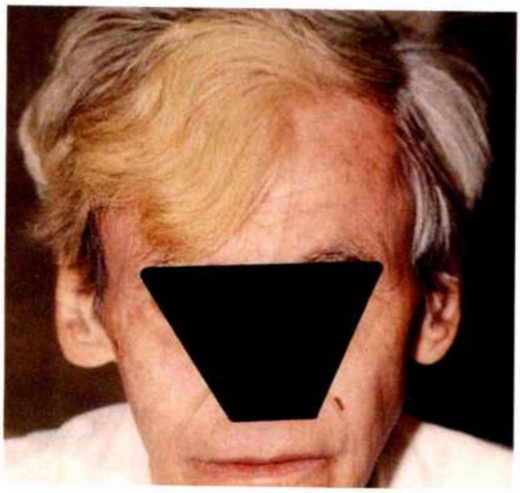
We examined a middle-aged man with a prominent yellow forelock who complained of loss of vision in both eyes. He smoked his pipe avidly and drank a little Bourbon whisky daily. The nicotine content of the forelock (21·7 ng/mg) was 10 times that of the hair on his occiput (2·23 ng/mg). A yellow forelock when associated with isolated painless visual loss suggests tobacco amblyopia.

For the diagnosis of tobacco-alcohol amblyopia Traquair required a history of smoking tobacco, visual loss in both eyes, centrocaecal scotomas with sloping edges containing one or more nuclei, and no changes in the peripheral field.[1]

We report the case of a late middle-aged man who smoked a pipe heavily most of his life, had visual loss in both eyes, and had a yellow forelock. We believe he represents a case of tobacco-alcohol amblyopia occurring in the United States of America.

Case report

A 63-year-old white man, a retired auditing clerk, complained of progressive painless loss of vision in both eyes for two months before we saw him. He had no other neurological complaints, and he denied weight loss. Past ocular history and family history were unremarkable. He smoked a pipe, consuming about 10 oz (280 g) of pipe tobacco per week for more than 15 years. Although he drank 1–2 'shots' (25–50 ml) of Bourbon whisky per day, he denied exposure to home-brewed alcohol, drugs, or industrial toxins. He lived alone and denied any food faddism. He was thin, looking older than his years; his gray hair had a prominent yellow forelock (Fig 1). He weighed 46·8 kg and was 167·6 cm tall (72% of ideal body weight). His best-corrected visual acuity was 'finger counting' as 4 feet (1·2 m) in both eyes. He identified only the control plate of the Ishihara pseudoisochromatic test. Both pupils reacted sluggishly to light (from 5 mm to 4 mm) without a relative afferent pupillary defect. The near reflex produced a final miosis of 2·5 mm in both eyes. Kinetic visual fields showed bilateral caecocentral scotomas (Fig 2). Both optic discs were pale temporally, and in the papillomacular bundle the nerve fibre layer was thin. The rest of the findings on ophthalmic examination were unremarkable.



[redacted]

Figure 1: The patient is a 63-year-old white man with gray hair and a prominent yellow forelock.

We found mild bilateral sensorineural hearing loss, but his deep tendon reflexes were normal, toe responses were flexor, and there were no signs of cerebellar dysfunction. His mental status was normal.

Laboratory studies included a normal haematocrit (41·7%) with a mean corpuscular volume of 113·5 fl (normal range 80–97·6). The smear showed <5% hypersegmented polymorphonuclear white blood cells. The vitamin B-12 level was 129 pmol/l (normal >140 pmol/l). Parietal cell antibodies were positive, with a low titre of 1:40. There were no intrinsic factor antibodies, and serum and red cell folate levels were normal. Blood urea nitrogen (BUN) was 2·1 mmol/l (3·7–7·0), albumin 42 g/l (35–48), and uric acid 210 μmol/l (240–540). Serum iron was 17·2 μmol/l (11–30), and the total iron binding capacity was 37 μmol/l (45–72). Transketolase assay and the lead level were normal. We could not assess the results of the Schilling test because the patient did not collect complete urine samples. He refused any determination of gastric pH. We could not find evidence of syphilis (VDRL, TPHA, and FTA-Abs tests were negative). He refused lumbar puncture or neuroimaging.

The nicotine content of his yellow forelock was 21·7 ng/mg but that of the hair from the back of his head was 2·23 ng/mg.

We diagnosed optic neuropathy due to tobacco abuse and treated him with 1000 μg/week of parenteral hydroxycobalamin and gave him oral multivitamins, including 100 mg of thiamine and 1 mg of folate daily. Over the next three months his vision did not improve. He still smoked his pipe but said that he had 'cut it down'.

We concede that given the available data (no cerebrospinal fluid examination or neuroimaging) we cannot prove unequivocally that this man had tobacco amblyopia. Nevertheless the clinical picture is suggestive and conforms to other descriptions.[1-5] We describe a physical sign not recorded before which indicates an addiction to tobacco: the yellow forelock. It reminds us of the white forelock seen in Waardenburg's syndrome.[6]

Washington University School of Medicine, St Louis, Missouri, USA, Department of Ophthalmology
R I Kellen
R M Burde

Department of Neurology
B Schrank
R M Burde

Department of Neurological Surgery
R M Burde

Correspondence to:
Ronald M Burde, MD,
Department of
Ophthalmology, Albert
Einstein College of
Medicine/Montefiore
Medical Center, 111 East
210th Street, Bronx, NY
10467, USA.

Accepted for publication
9 January 1990

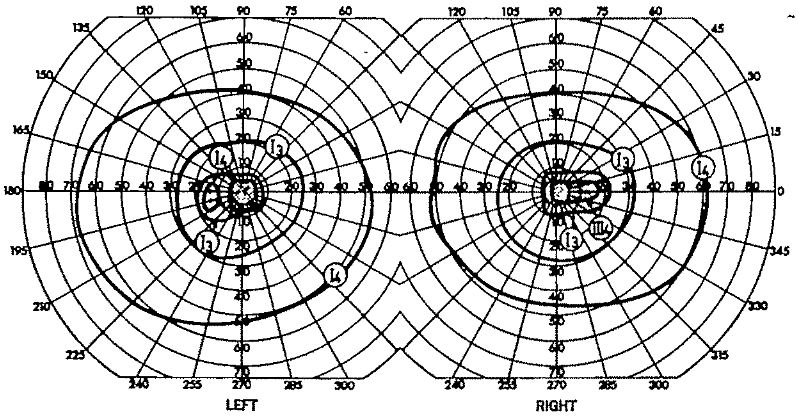


Figure 2: Kinetic visual fields showing bilateral caecocentral scotomas.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc , New York, New York (Department of Ophthalmology).

1 Traquair HM. Toxic amblyopia, including retrobulbar neuritis *Trans Ophthalmol Soc UK* 1930, 50: 351–95.
2 Wokes F. Tobacco amblyopia. *Lancet* 1958; ii: 526–7.
3 Foulds WS, Chisholm IA, Bronte-Stewart J, Reid HCR. The investigation and therapy of the toxic amblyopias *Trans Ophthalmol Soc UK* 1970, 90: 739–63
4 Potts AM Tobacco amblyopia *Surv Ophthalmol* 1973; 17: 313–39
5 Foulds WS, Pettigrew AR. Tobacco-alcohol amblyopia. In: Brockhurst RJ, Boruchoff SA, Hutchinson BT, Lessell S eds. *Controversies in ophthalmology* Philadelphia; Saunders, 1977: 851–65.
6 Waardenburg RJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness *Am J Hum Genet* 1951; 3: 195–253.

BOOK REVIEW

Dictionary of Visual Science. 4th Edn. By David Cline, Henry W Hofstetter, John R Griffin. Pp 820. US$57. Chilton Trade Book Publishing: Radnor, Pennsylvania, 1989.

The 4th edition of this book, first published almost 30 years ago, is dedicated to the memory of the late senior editor described as the motivator of this lexicographic work. The majority of the 68 contributors are optometrists or basic scientists, with a mere handful of clinicians. Not surprisingly, there is a certain bias towards optometric terminology, and indeed the strength of the book lies in its coverage of physical and geometrical optics, ophthalmic dispensing, and vision therapy. As stated in the preface, this edition extends the coverage of ocular genetics, pharmacology, familiar and unfamiliar acronyms, and abbreviations and syndromes with ocular manifestations.

On the whole the clinical listings are rather disappointing and somewhat limited, with inclusion of many obsolete terms and nomenclature. As intended, the definitions are generally succinct, and a phonetic respelling follows most entries. There are very few listings accompanied by their derivation, which is somewhat disappointing. Throughout the text there is a random selection of line diagrams depicting mostly optical principles and equipment with photographs of clinical disorders, many of which are of poor quality. Clinical terms can prove difficult to find, and eponymous titles are listed under disease, syndrome, or anatomical structure. There is a wealth of archaic clinical terms which offer a certain fascination and would be guaranteed to floor or possibly demolish an unsuspecting examination candidate. There is a brief appendix including ophthalmic clinical abbreviations, symbols, and useful optometric data. Although the dictionary has a number of shortcomings, it will nonetheless prove a useful reference manual for all workers in the field of visual science.

ROBERT J COOLING

LETTERS TO THE EDITOR

Carbamazepine, epilepsy, and optic nerve hypoplasia

Sɪʀ,—We report a case of bilateral optic nerve hypoplasia (ONH) in a child born to a woman taking carbamazepine (CBZ) during pregnancy. A mother of two healthy girls developed generalised seizures at the age of 27 years. She has remained on CBZ (1 g/day) monotherapy since then and has had no further seizures. During her third pregnancy (aged 29 years) she was admitted to hospital at 17 and 20 weeks for blood loss, which settled uneventfully. At 39 weeks she had a normal delivery of a healthy 4 kg girl.

Initial ophthalmic examination of the baby at nine weeks showed roving eye movements. Pendular nystagmus and a right convergent squint have subsequently developed. Examination under anaesthetic at five months revealed isolated extremely small hypoplastic optic nerves. A computed tomographic brain and orbital scan was unremarkable apart from abnormally slender optic nerves. At eight months visual function remains severely impaired. The baby is otherwise developmentally and physically normal.

Possible teratogenic effects of anticonvulsant drugs during pregnancy have been reported for more than 20 years. The fetal hydantoin syndrome has been primarily associated with phenytoin. It combines poor growth with mild mental retardation, a characteristic craniofacial appearance, and skeletal abnormalities, including digital hypoplasia. It is said to occur in 11% of at-risk infants. Incomplete forms are known to occur in another 31%. The number of isolated malformations described following fetal phenytoin exposure are protean and includes ONH in seven previously described cases.[1] The relative contributions of the epilepsy and anticonvulsants to the described abnormalities are disputed, though phenytoin has been shown to be teratogenic in experimental animals. Furthermore there is evidence that combinations of hydantoins and barbiturates may increase the risk to the fetus.

CBZ in high doses has been shown to reduce fetal body and brain weight in pregnant mice.[2] In 1973 Starreveld-Zimmerman *et al.*[3] observed no congenital malformations in 50 CBZ exposed babies and 22 malformations in 247 babies whose mothers had taken anticonvulsants other than CBZ, but Hiilesmaa *et al.*[4] subsequently described fetal head growth retardation in babies born to mothers taking CBZ.

While many cases of ONH are idiopathic, several substances have been implicated as causative. They include quinine, lysergic acid diethylamide (LSD), phencyclidine, alcohol, and phenytoin.[5] There is also an increased incidence of ONH in infants born to diabetic mothers.[5]

Numerous studies now suggest that susceptibility of the fetus to teratogenic effects of hydantoins depends on the fetal genotype. Inherited defects in phenytoin arene oxide detoxification may contribute. As CBZ and phenytoin are structurally different, it is not possible to postulate a similar pathogenic mechanism for ONH development in the former.

To our knowledge, the occurrence of isolated ONH in association with CBZ monotherapy is unique. Could they be causally related, or is this a chance occurrence?

JAMES WEST
JOHN P BURKE
IAN STRACHAN
*Department of Ophthalmology,
Royal Hallamshire Hospital,
Sheffield S10 2JF*

1 Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978; 62: 3–6
2 Fritz H, Muller D, Hess R Comparative study of the teratogenicity of phenobarbitone, diphenylhydantoin and carbamazepine in mice. *Toxicology* 1976, 6: 323–30.
3 Starreveld-Zimmerman AAE, Van der Kolk WJ, Meinardi H, Elshove J. Are anticonvulsants teratogenic? *Lancet* 1973; ii: 48–9
4 Hiilesmaa VK, Teramo K, Granstrom ML, Bardy AH Fetal head growth retardation associated with maternal antiepileptic drugs. *Lancet* 1981, ii: 165–7.
5 Lambert SR, Hoyt CS, Narahara MH Optic nerve hypoplasia. *Surv Ophthalmol* 1987; 32: 1–9

Intravitreal therapy with ganciclovir for posterior pole cytomegalovirus retinitis in AIDS patients

Sɪʀ,—Several authors have reported the use of intravitreal ganciclovir therapy for patients with cytomegalovirus retinitis (CMV).[1-5] The associated complications due to this therapy are substantial and include subconjunctival haemorrhage, laceration of the lens by the needle during injection, retinal detachments secondary to iatrogenic tears, vitreous haemorrhage, and endophthalmitis. Despite these shortcomings some authors have been encouraged by its ability to improve CMV retinitis.[1,3,5]

We have treated eight eyes in five patients with severe involvement of the posterior pole (optic nerve-macula region) who also had severe neutropenia which precluded their continued treatment with systemic ganciclovir at normal levels. Treatment consisted of a series of three intravitreal 200 µg injections, which was administered through the pars plana region of the eye under retrobulbar anaesthesia every five days during a 15-day period. A 30 gauge short needle on a tuberculin syringe was used. Thereafter the injection was administered once per week until the appropriate intravenous induction (5 mg/kg intravenously twice a day) or maintenance (5 mg/kg intravenously four times a day) dosage could be resumed. We found that this therapy was useful only as an adjunct to the systemic dosage. By itself the injections were not able to improve clinically either the retinitis or the visual acuity. However, the retinitis ceased to advance and the acuity stabilised when intravitreal ganciclovir was given concomitantly with the systemic ganciclovir. Retrobulbar anaesthesia should be used to ensure that the patient does not experience pain during the injection. Sudden movement of the patient during the injection may lead to complications noted by several authors.[4,5]

We feel that intravitreal ganciclovir by itself will not improve CMV retinitis of the posterior pole. It must be administered with systemic ganciclovir, even in a reduced dosage, in order to at best stabilise the retinitis.

J ORELLANA
R M LIEBERMAN
R PEAIRS
S RESTREPPO
*944 Park Avenue, New York,
New York 10028 USA*

1 Ussery III FM, Gibson SR, Conklin AJ. Intravitreal ganciclovir in the treatment of AIDS-associated cytomegalovirus retinitis. *Ophthalmology* 1988; 95: 640–8.
2 Buchi ER, Fitting PL, Michel AE Long-term intravitreal ganciclovir for cytomegalovirus retinitis in a patient with AIDS. *Arch Ophthalmol* 1988, 106: 1349.
3 Henry K, Cantrill H, Fletcher C, Chinnock BJ, Balfour Jr HH. Use of intravitreal ganciclovir (dihydroxy propoxymethyl guanine) for cytomegalovirus retinitis in a patient with AIDS *Am J Ophthalmol* 1987; 103: 17–23
4 Cantrill HI, Henry K, Melroe NH, Knobloch WH, Ramsay RC, Balfour HH Treatment of cytomegalovirus retinitis with intravitreal ganciclovir. Long-term results. *Ophthalmology* 1989; 96: 367–74
5 Harris ML, Mathalone MBR Intravitreal ganciclovir in CMV retinitis case report. *Br J Ophthalmol* 1989; 73: 382–4

Viscoelastic agents in ocular surgery

SIR,—Lavin and Khaw have drawn attention to the use of viscoelastic agents for improving visualisation during ocular surgery.[1] One problem that occurs is when during ocular examination or surgery the internal view is obscured by phenylephrine epitheliopathy.[2] A use for hydroxypropylmethyl cellulose (HPMC) 2%, not mentioned by Lavin and Khaw, is when during ocular examination or surgery the internal view is obscured by phenylephrine epitheliopathy.[2,3] Application of a layer of HPMC 2% or sodium hyaluronate to the cornea results in a marked improvement in corneal clarity, which may be enough to prevent epithelial debridement having to be performed.

J D STEVENS
Moorfields Eye Hospital,
City Road, London EC1V 2PD

1 Lavin MJ, Khaw PT Use of viscoelastic agents to aid visualisation during ocular surgery *Br J Ophthalmol* 1990; 74: 192
2 Edelhauser HF, Hine JE, Pederson H, Van Horn DL, Schultz RO The effect of phenylephrine on the cornea *Arch Ophthalmol* 1979, 97: 937–47
3 Machemer R, Aaberg TM *Vitrectomy*. 2nd ed. In Machemer R, Aaberg TM, eds. New York Grune and Stratton, 1979 33.

Reply

SIR,—We did not specifically mention phenylephrine epitheliopathy when we outlined the use of hydroxypropylmethylcellulose (HPMC) to prevent corneal opacification, but would fully agree with Mr Stevens. In our experience the use of HPMC does improve the view through the cornea which may otherwise be obscured by topical drug induced epitheliopathy. With the use of HPMC on the cornea we have never had to perform an epithelial debridement on an eye with eyedrop-induced epitheliopathy during cataract surgery.

P T KHAW
Institute of Ophthalmology,
Cayton Street,
London EC1V 9AT
M J LAVIN
Moorfields Eye Hospital,
City Road,
London EC1V 2PD

Two new titles from the BMJ's series of books of general interest by medical writers

The
MEMOIR
Club

Not a Moment to Lose *by Sir David Smithers*

Sir David Smithers, former president of the British Institute of Radiology and of the Royal College of Radiologists, was for 30 years professor of radiotherapy at the Royal Marsden Hospital. But that is only half the story. He is also a man who believes that "one should aspire to be a realist but retain a sense of wonder, a rationalist who is prepared to jump to conclusions, and a critical visionary who remains sensible of the humour of the human situation". Recounting how he has lived according to these principles, David Smithers describes, in addition to his medical career, his experiences as a broadcaster, traveller, rose grower, and observer of human nature.

Inland £14.95; Abroad £17.50. BMA members: Inland £13.95; Abroad £16.50

)ne Man's Medicine *by Professor Archie Cochrane with Max Blythe*

\rchie Cochrane was one of Britain's most influential thinkers on health care nd the quality of health services. His 30 years' association with the Rhondda ach—and his work there on reducing the suffering inflicted on whole ommunities by pneumoconiosis—is almost legendary. Ironically, this was early overshadowed later in his life by the spectacular success of his Rock arling monograph *Effectiveness and Efficiency,* which proved to be a seminal vork and influenced thinking about the assessment of medical treatment and rocedures throughout the world.

What kind of man was he, and what led him to such a career? In *One Man's ledicine* (written in collaboration with Max Blythe) Archie Cochrane recalls vith candour and perception the dilemmas and disasters that beset his early mbitions for a career in clinical medicine and research; his undergoing sychoanalysis with Theodor Reik in Germany in the early 1930s; his support for he republicans in Spain; and his four years as a prisoner of war in Salonica (for which he usually blamed Evelyn Waugh).

A rich and rewarding book, *One Man's Medicine* sums up the life and opinions f a remarkable man.

nland £14.95; Abroad £19.00 BMA members: Inland £13.95; Abroad £18.00

Crown copyright
The x-ray service of the Medical Research Council's Pneumoconiosis Research Unit visiting Tylorstown pithead in 1950.

ogether with the Nuffield Provincial Hospitals Trust, the BMJ has reprinted *ffectiveness and Efficiency.* This new edition also includes a brief note written by Archie ochrane reflecting upon the monograph some two years after its publication, and the bituary written with such honesty by himself.

nland £9.95; Abroad £12.50 BMA members: Inland £8.95; Abroad £11.50

)RDER FORM British Medical Journal, PO Box 295,
London WC1H 9TE, England *or any leading bookseller*

lease send me the following books:

The
MEMOIR
Club

☐ **Not a Moment to Lose**
☐ **One Man's Medicine**
☐ **Effectiveness and Efficiency**

Prices to include postage, by air abroad

AME ....
ase print name and address clearly
DDRESS ....
....
)ST CODE ....

☐ I enclose .... BMA Membership No. ....

Please make cheques payable to British Medical Journal or debit my credit card (*please tick box*)

☐ VISA ☐ AMERICAN EXPRESS ☐ MASTERCARD

CARD NUMBER ____________________

Card expiry date ....

Signature ....

☐ Please send me a details of previous Memoir Club books

Did ed, BMJ, murder his wife?

Supposedly based on rumoured events in the life of Ernest Hart, a great but undervalued editor of the *BMJ,* Frank Danby's novel *Dr Phillips: a Maida Vale Idyll* was first published in 1887. Unlike many popular Victorian novels it is concisely plotted; its style is pithy; the characters are sympathetic and believable; and the author's presentation of Jewish life in the late nineteenth century is uncompromisingly honest. But is the character of "Dr Phillips" a portrait of Hart? In his introduction to the new Keynes Press edition Stephen Lock, present editor of the *BMJ,* places the novel in its literary and historical context and examines the character and achievements of Ernest Hart.

Beautifully printed and bound, and with illustrations by Tabitha Salmon, this edition of *Dr Phillips: a Maida Vale Idyll* will fascinate those interested in literature, history, and the *BMJ.*

Dr Phillips

A Maida Vale Idyll

FRANK DANBY

Published December 1989
Demy octavo; set in Monophoto Modern
and printed on Fineblade Cartridge paper;
xii + 285 pages + colour frontispiece
Limited edition of 300 copies
Inland £45.00; Abroad £49.00; USA $80.00
including postage, by air abroad
American Express, Mastercard, Visa credit cards
accepted. Please give full details.
British Medical Journal, (Keynes Press), PO Box 295,
London WC1H 9TE

THE
KEYNES
PRESS

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- **24 hour delivery.**
- **Courier services.**
- **Personal delivery.**

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia
Advancing The New Biology

NEW FORMULATION
When
nature runs dry . . .
HYPOTONIC
LIQUIFILM®
polyvinyl alcohol
TEARS
NEW HYPOTONIC FORMULATION
to help restore normal tearfilm tonicity
in lipid, aqueous and mucin deficient eyes[1]
FOR SUCCESS FROM THE START – FIRST TIME

Liquifilm Tears Prescribing Information

Presentation: Clear, colourless to slightly straw-coloured, sterile, aqueous ophthalmic solution containing Liquifilm (polyvinyl alcohol) USP 1.4% (w/v). Also contains disodium edetate Ph Eur 0.015% (w/v), benzalkonium chloride Ph Eur 0.005% (w/v) with sodium chloride Ph Eur, sodium phosphate Ph Eur and purified water Ph Eur. **Uses:** Liquifilm Tears is an ocular lubricant for the relief of dry eye and dry eye symptoms. **Dosage and administration:** For all ages. One or two drops administered topically to the affected eye(s) as required. **Contra-indications, warnings etc:** *Contra-indications:* Sensitivity to any of the components. Not for use with soft (hydrophilic) contact lenses because of the presence of benzalkonium chloride as a preservative. *Warnings:* If irritation increases or persists, discontinue use. **Pharmaceutical precautions:** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category:** P. **Package quantities:** LIQUIFILM TEARS is available in plastic dropper bottles containing 15 ml. **Basic NHS Cost:** (as at November 1988) £1.33. **Further Information:** Nil. **Product Licence Number:** PL 0426/0009R. **Date of preparation:** July 1988. **Reference:** 1. Bron AJ. Trans Ophthalmol Soc U.K. (1985); **104**: 801-826.

ALLERGAN PHARMACEUTICALS
TM
SCIENCE WITH VISION

Full prescribing information is available on request.
Allergan Limited, High Wycombe, Bucks. HP12 3SH. ®denotes registered trade mark

22.4.91

SEPTEMBER 1990 VOL 74 NO 9

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

513 Lye in the eye *Redmond Smith*

Original articles

514 Eye injuries from assault with chemicals *John D L Beare*

519 Staining of the conjunctiva and conjunctival tear film *Joseph A Eliason, David M Maurice*

523 Acute closed-angle glaucoma and Nd-YAG laser iridotomy *D C Saunders*

526 Influence of pupil size on measurements made with the Lens Opacity Meter 701 *Michael P Clarke, James C G Pearson, Stephen A Vernon, J Colin Matthews*

528 Topical steroids in the treatment of central and paracentral corneal ulcers *T R Carmichael, Y Gelfand, N H Welsh*

532 Antiviral drug sensitivity in ocular herpes simplex virus infection *M J Menage, E de Clercq, A van Lierde, V S Easty, J M Darville, S D Cook, D L Easty*

536 Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis *Richard F Spaide, John E Skerry, Lawrence A Yannuzzi, Janet T DeRosa*

538 Radioimmunoscintigraphy and immunohistochemistry with melanoma-associated monoclonal antibodies in choroidal melanoma: a comparison of the clinical and immunohistochemical results *D F Schaling, J P van der Pol, M J Jager, M J P G van Kroonenburgh, J A Oosterhuis, D J Ruiter*

542 Congenital eyelid retraction *J R O Collin, L Allen, S Castronuovo*

545 The volume-deficient orbit: clinical characteristics, surgical management, and results after extraperiorbital implantation of Silastic block *Geoffrey E Rose, Harold Sigurdsson, Richard Collin*

551 Experimental *Acanthamoeba* keratitis: I. Preliminary findings *D F P Larkin, D L Easty*

556 Computerised visual field deficits in tears of the retinal pigment epithelium *Joseph I Maguire, William H Annesley Jr, William L Decker, Gary C Brown, David H Fischer, Joan M Slagle*

Mini review

559 Management of intraocular melanoma *Wallace S Foulds*

Case reports

561 A case of fungal keratitis caused by *Scopulariopsis brevicaulis*: treatment with antifungal agents and penetrating keratoplasty *Nicola K Ragge, J C Dean Hart, D L Easty, A G Tyers*

563 Traumatic hyphaema in a haemophiliac *C D G Morsman, J Holmes*

564 Spontaneous reabsorption of a rubella cataract *George T H Smith, G Adrien Shun-Shin, Anthony J Bron*

566 Progression of an iris melanoma over 41 years *David G Charteris*

568 11p13 Deletion, Wilms' tumour, and aniridia: unusual genetic, non-ocular and ocular features of three cases *Véronique Jotterand, Hélène M Boisjoly, Carmen Harnois, Pierre Bigonesse, Rachel Laframboise, Richard Gagné, André St-Pierre*

571 Self-enucleation and psychosis *Nicholas P Jones*

574 Lymphangioma circumscriptum of the eyelids and conjunctiva *R R Goble, M A Frangoulis*

576 **Letters to the editor Note Fifty years ago**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE

Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Journal

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced*.

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof, and should read it carefully for printers' errors. Alterations to the original text should be kept to a minimum and may be charged to the author.

REPRINTS may be ordered from the Publishing Manager when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Ophthalmology*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not, however, required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents of the publication without prior permission is always illegal.

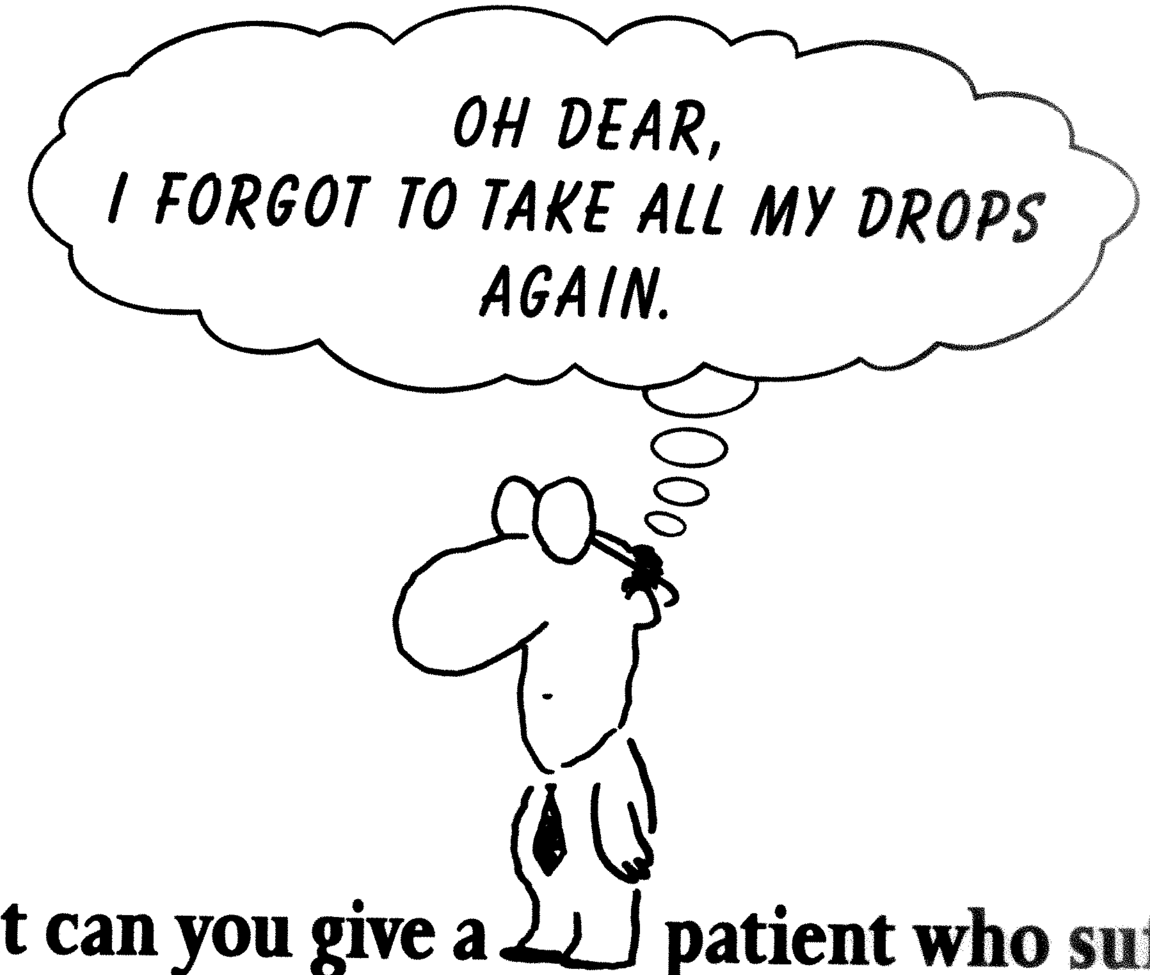
NOTICE TO ADVERTISERS Applications for advertisement space and for rates should be addressed to the Advertisement Manager, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *British Journal of Ophthalmology* is published monthly. The annual subscription rates are £106.00 inland and £126.00 overseas (US $200.00). Orders should be sent to the Subscription Manager, British Journal of Ophthalmology, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. All inquiries regarding air mail rates and single copies already published should be addressed to the Publisher in London.

Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd


OH DEAR,
I FORGOT TO TAKE ALL MY DROPS
AGAIN.

What can you give a patient who suffers from amnesia as well as glaucoma?

Getting patients to comply with complicated ose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, he beta blocker most patients only need to take nce a day. This is possible because of Betagan's ustained activity over 24 hours,[1] hich has been shown to be ffective in controlling the traocular pressure of up to % of patients on a once aily dose.[2]

In fact, in a study evaluating once-daily Betagan the authors concluded "once-daily treatment with levobunolol appeared to be as effective as twice-daily treatment while offering greater convenience and comfort and potentially greater safety."[3] So next time you're looking for a simple but flexible treatment for open angle glaucoma, consider Betagan.

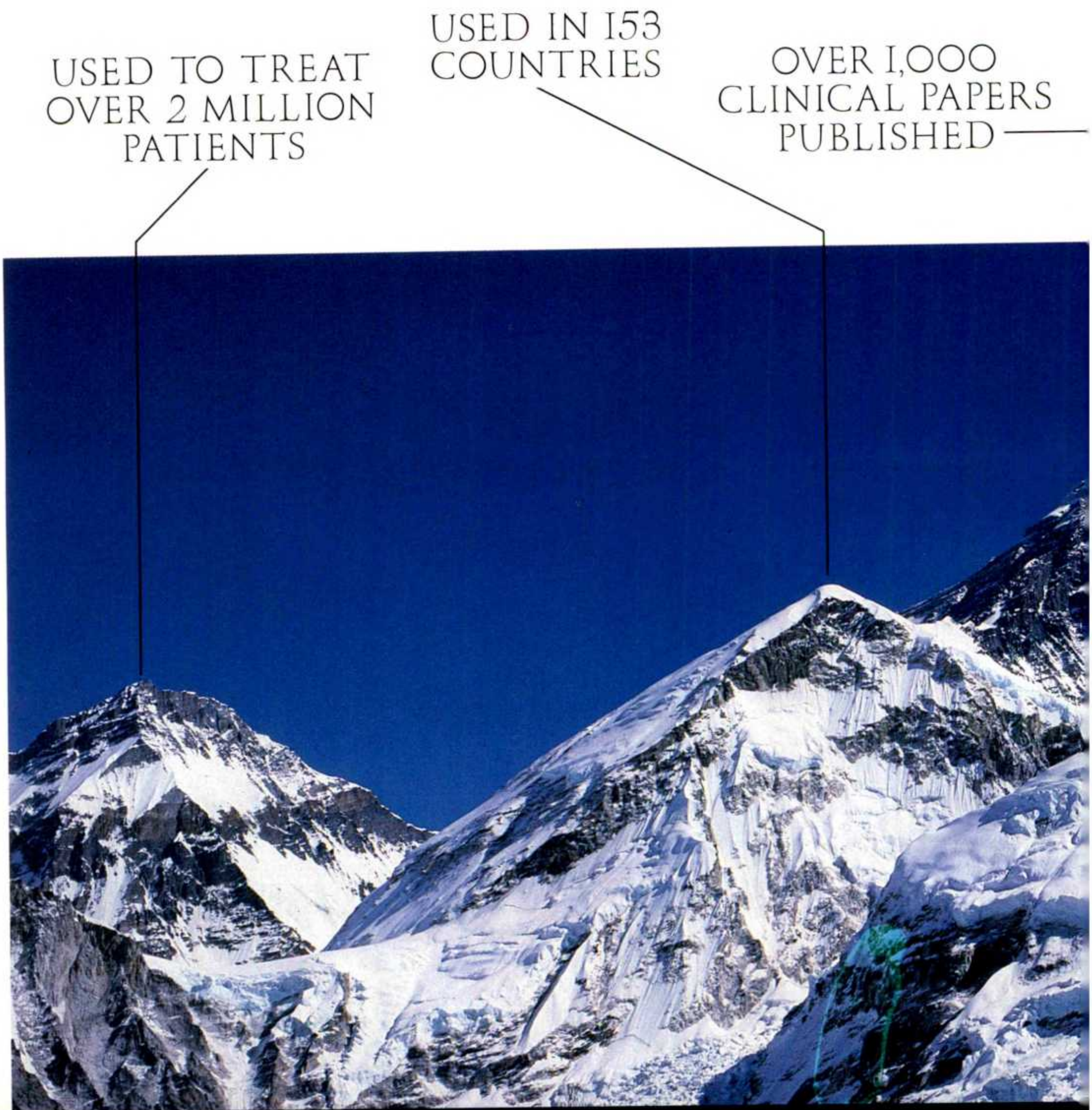
It's a name worth remembering.

BETAGAN®
(levobunolol hydrochloride 0.5%)
ONCE DAILY

ONE DROP THEY WON'T FORGET

PRESCRIBING INFORMATION
ESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v). **ACTION:** Beta-adrenergic blocking agent. **INDICATIONS:** Reduction of raocular pressure in chronic open-angle glaucoma and ocular hypertension. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:** Contraindications: Bronchial hma; history of bronchial asthma; chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block; cardiac failure; cardiogenic ock; hypersensitivity to any component. Caution in labile diabetes and in patients receiving oral beta-adrenergic blocking agents. Do not use in patients continuing to wear drophilic (soft) contact lenses. Transient ocular burning and stinging on instillation may occur. Bradycardia, potension, dyspnoea and asthma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) e or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE: £5.05** 0426/0060. Full prescribing information is available on request.
uzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11.
Vandel, T. *et al.*, Am J Ophthalmol 1986; *101*: 298-304.

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.
® Betagan is a registered trade mark.


USED TO TREAT OVER 2 MILLION PATIENTS
USED IN 153 COUNTRIES
OVER 1,000 CLINICAL PAPERS PUBLISHED

WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-block should be withdrawn gradually.

Do not use in patients with soft contact lens Mydriasis resulting from use of 'Timoptol' with adr aline reported occasionally. Potentially, hypotensi and/or marked bradycardia may result from additi of 'Timoptol' to a calcium antagonist, rauwol alkaloid or beta-blocker.

Children: Not recommended. Data not available use in children. *Nursing:* Mother should either s nursing or stop 'Timoptol'. *Pregnancy:* Not studi weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, blep

12-90 TOT.89.GB.4697.J.

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
OPEN-ANGLE GLAUCOMA
HERAPY BY THE MAJORITY
F UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE

TOP 'TIMOPTOL'?

is, keratitis, blepharoptosis, and decreased corneal sitivity. Visual disturbances, including refractory nges (due sometimes to withdrawal of miotics), lopia, and ptosis.

dycardia, arrhythmia, hypotension, syncope, rt block, cerebrovascular accident, cerebral haemia, congestive heart failure, palpitation, diac arrest.

nchospasm (predominantly with pre-existing nchospastic disease), respiratory failure, dyspnoea.

adache, asthenia, nausea, dizziness, depression.

persensitivity, rash, and urticaria.

ctions with an unestablished relationship are MO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST

0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack. 0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

Product licence numbers:

0.25% Ophthalmic Solution 'Timoptol', 0025/0134.
0.5% Ophthalmic Solution 'Timoptol', 0025/0135.

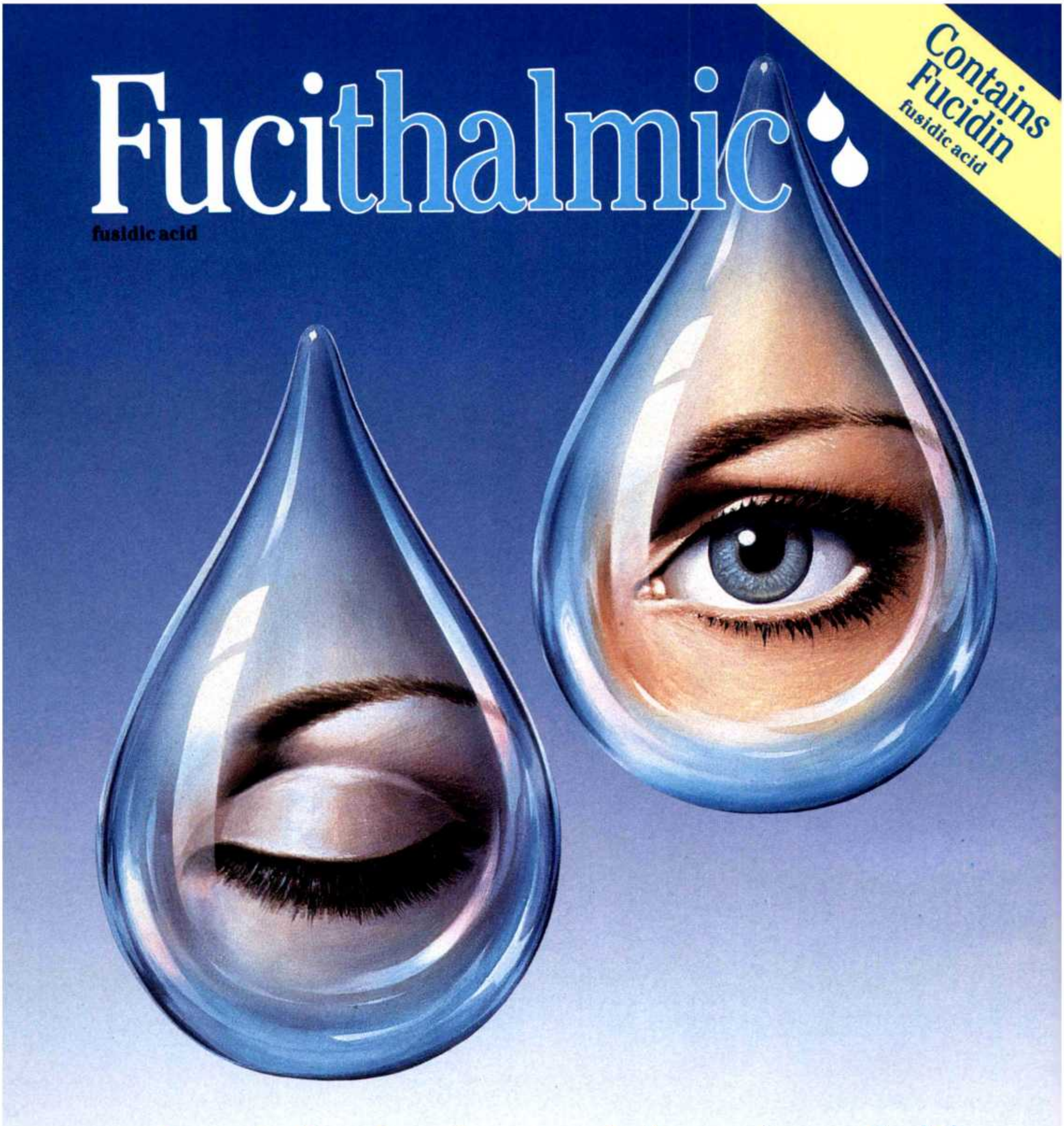
® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference

1. Data on file, Merck Sharp & Dohme Limited.

Ophthalmic Solution
Timoptol®
(timolol maleate, MSD)

JNSURPASSED AS FIRST-LINE GLAUCOMA THERAPY


Fucithalmic
fusidic acid
Contains Fucidin fusidic acid
twice daily for bacterial conjunctivitis

▼ Prescribing Information.

Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses:** Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications:** Bacterial conjunctivitis due to sensitive organisms. **Dosage:** One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications:** Hypersensitivity to any component. **Precautions:** Should not be used when contact lenses are being worn. **Side effects:** Transient stinging. Hypersensitivity may occur. **Product Licence Number:** 0043/0137. **Basic N.H.S. Price:** £2.25/5g tube.

L E O

Further information available on request:

Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Lye in the eye

I seem to remember that years ago assaults leading to chemical injuries of the eyes in the USA were often described as having been carried out with a substance known as lye. American authors seemed to take it for granted that everyone knew what lye was, though it was certainly not obvious to me and perhaps to others. I had a vague idea that it was the strongly alkaline soup of caustic soda and fat that was eventually to be precipitated out as soap. Reading the article at page 514 of this month's issue on chemical injuries prompted me to look up the definition of lye, and when I discovered that it was simply caustic soda or potash in solution I realised that I had for years been labouring under a delusion on the subject. However, the encyclopaedia's description of soap manufacture does also refer to lye in the sense I alluded to above, so I was not completely wrong.

Searching for inspiration about the subject of chemical injuries one cannot do better than to turn to the classic textbook of the 1950s by Sir Stewart Duke-Elder.[1] Here we find a dramatic account of the clinical features and the pathology of a great variety of chemical and in particular alkali injuries, together with a photograph of a lye burn of the human eye. Better still there is even a definition of lye: 'the solution of the hydroxides (potash or soda lye).' But the interesting thing about Duke-Elder's account, not only of lye but also of the more rapidly blinding ammonia, is that he makes little mention of assault, the whole thrust of the chapter (which incidentally is dedicated to Herman Knapp, the father of American ophthalmology) being directed towards accidents, either domestic or industrial.

In a brilliant account of the incidence of chemical injuries in which he concludes that 'Industry is responsible for the vast majority of chemical hazards' the author does concede that the eyes may be made the object of deliberate chemical attack by 'the distraught or malignant woman who desires to disfigure the face of the object of her jealousy or revenge with acid, by the policeman who attempts to quell mob violence with lacrimatory gas, or by the army which makes war still more horrible than it used to be by attempts to overwhelm a foe with poison gas or vesicants'. Robbery and random assaults in the street are not mentioned.

Since Duke-Elder's technique consisted of the compilation of information from an enormous number of sources, it is unlikely that he would have missed a significant number of papers on street assault with chemical eye injuries. Thus the suggestion by the authors in this month's paper that such injuries are on the increase is probably correct.

It is uncertain whether in some of the assaults, where sheer mischief seems to be the motive rather than any more directed reason such as robbery or personal animosity, the assailants realise how much damage they may be doing. It is difficult to know whether educating the public about the possibility of permanent blindness following assaults of this nature would put the attackers off or encourage them. As the authors mention, the psychological effects on the victims can be very bad. I had a case some years ago where ammonia was used in a bank robbery, and the victim, who suffered acute lens swelling and other injuries, finally took his own life. Mortality is not a statistic that we ophthalmologists often have to take much account of (unless we are oncology experts), but it seems to be a distinct possibility in some of the more severely affected patients after chemical assaults causing blindness.

An afterthought: the word 'blinding' when used by journalists or novelists to describe an attack is usually understood to mean 'temporarily blinding'. One wonders how many people realise that in some cases, particularly where ammonia is used, the blinding may be far from temporary. In considering the effect this knowledge might have on criminals I forgot to mention that the same misconception might be held by some judges and magistrates. One hopes that members of the legal profession, and the police as well, are as aware of the deadly nature of ammonia and like substances as are ophthalmologists.

REDMOND SMITH

---

1 Duke-Elder WS *Textbook of ophthalmology*. London Kimpton, 1954· 6: 6581–9.

ORIGINAL ARTICLES

Eye injuries from assault with chemicals

John D L Beare

Abstract

Sixty four patients with eye injuries resulting from assault with chemicals were reviewed. In 17 eyes of 16 patients there was total corneal epithelial loss with varying degrees of limbal ischaemia. Nine eyes were effectively blinded and two eyes suffered less severe but permanent impairment of vision.

Direct contact of noxious chemicals with the eye can cause severe eye injuries. Alkalis are particularly harmful.[1-10] We have seen a marked increase in the number of patients presenting with eye injuries resulting from assault with chemicals over the past six years.[11] This trend has also been noted at other hospitals in London.[12] Only one case was seen in 1984, increasing to three cases in 1985, 15 cases in 1986, 37 cases in 1987, and 40 cases in 1988. The total fell again to 15 cases in 1989 (Fig. 1). The 15 assault cases seen in 1989 represented 8% of a total figure of 187 cases of chemical eye injury from all causes seen during that year. During the six-year period the total number of new patients seen per annum in the Accident and Emergency Department at the Western Ophthalmic Hospital has remained constant at about 8500. Figures supplied by the Metropolitan Police Office (personal communication, 1989) also show a gradual increase in the number of assaults involving a noxious substance in the Metropolitan District over the period 1980–1988 (Fig. 2).

Patients and methods

The Western Ophthalmic Hospital is a busy eye hospital in the West End of London with 20 333 patients seen in the Accident and Emergency department, and 29 853 patients seen in the outpatient department over the 12 month period January-December 1988. The hospital is situated on the edge of Paddington, a mainly residential area containing many different ethnic groups.

Diagnostic information on all new patients presenting to the Accident and Emergency Department over the past six years was retrieved from the booking-in ledgers. Information was obtained from the case notes of 64 patients seen between 1 January 1984 and 31 March 1988. Forty-four different parameters including the presenting ocular features, the circumstances of assault, and the severity of eye injury were recorded where possible. Twenty-six patients were seen personally by the author at presentation, while information on the presenting features of the remaining 38 patients was obtained retrospectively from the case notes.

Fifty four (85%) of the 64 patients were eventually reviewed by the author. Minimum follow-up time on these patients was nine months after injury.

Results

VICTIMS

Of the 64 patients 55 were male and 9 female (86% M:14% F). Their average age was 32 years (range 16–64). Approximately 10% of the victims were unemployed, 10% were students, 10% were visitors from overseas, and the remaining 70% were in full time employment apart from one housewife. The victims' occupations included a merchant banker, an electronics engineer, a computer programmer, a hospital pharmacist, and a chef.

Alcohol. At least 10 patients had been drinking heavily shortly before the assault. This was

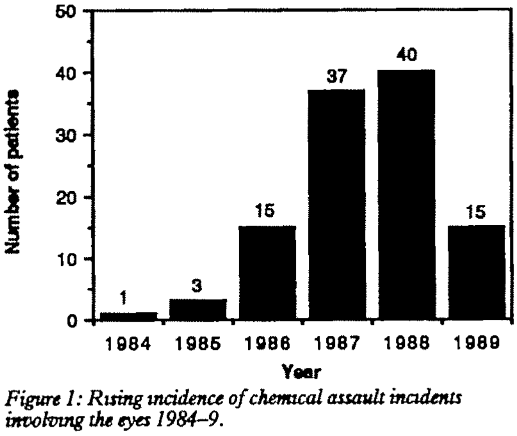


Figure 1: Rising incidence of chemical assault incidents involving the eyes 1984–9.

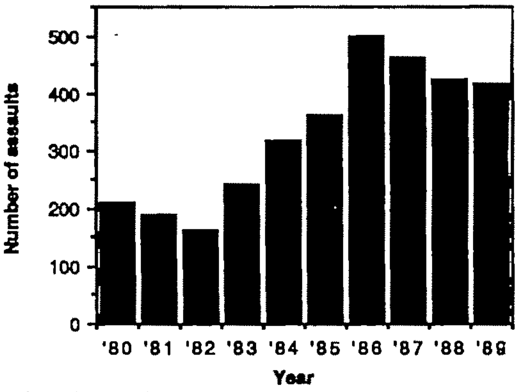


Figure 2: Assaults with a noxious substance in the Metropolitan Police District 1980–9.

Western Ophthalmic Hospital, London NW1 5YE
J D L Beare

Correspondence to:
J D L Beare, FRCS.

Accepted for publication
1 March 1990

particularly common in the more severely injured patients, whose inebriated state may have contributed both to their being selected as victims and also to the delay in washing out their eyes or seeking attention.

Time of injury. Injuries occurred particularly during the latter half of the year, with 73% of the 64 cases occurring during the four-months August-November during the 4½-year period. This appears to have been largely due to two clusters of cases in August 1986 (six cases) and August 1987 (15 cases) which occurred at the Notting Hill carnival. The carnival is an annual event attracting up to one million people which takes place in the streets of Notting Hill over a three-day period in August of each year. This trend has been less marked in 1988 with a more even spread of cases over the year, and indeed only three ocular chemical burns due to assault at the carnival were seen in August 1988. Assaults were also more common in the evening, at weekends, or on public holidays.

Place. Forty seven assaults occurred in the street. Four patients were assaulted in an underground station, four while waiting at a bus stop, three patients were attacked in a public house, and two were assaulted in their homes. Details were not available on the remaining four patients.

Other injuries. Injuries other than to the eye were uncommon, though one man was stabbed in the abdomen, requiring laparotomy for a perforation of the small bowel. Significant facial and lid skin burns occurred in six cases, though there were no cases of serious facial or lid skin necrosis. Two patients reported coughing, but no patients had any acute respiratory problems due to inhalation.

Symptoms. Intense stinging and pain in the eyes were the usual symptoms immediately after being sprayed.

Attackers. Only one victim (a heroin pusher) actually knew his attacker. The assailants were most frequently gangs of youths, from early teenage to twenties in age, numbering up to 12 persons, and were male in every case.

Method. One patient was assaulted by several teenagers on bicycles who mounted the pavement in order to attack him.

A liquid was sprayed or thrown in most cases. A Jif Lemon[12] was employed in four cases, an aerosol in five cases (probably containing a lacrimator such as Mace), and a child's water pistol was used in one case. In one case a white foam was sprayed from an aerosol.

Motive. The motive for the attack was usually unknown, though robbery occurred in 10% of cases. Most attacks were completely unprovoked and unexpected. Racial bias was a likely precipitant in several cases.

Chemical agents used in assault. The chemical agent used was usually not known, but six patients reported smelling ammonia shortly after the injury.

INJURIES

Thirty seven cases (58%) of eye injuries were unilateral, and 27 (42%) bilateral, making 91 eyes in total.

Irrigation. The time interval between injury and first irrigation ranged from 5 seconds to 12 hours. Several patients were inebriated by alcohol at the time of injury and did not seek medical attention until the following day. Irrigation was often performed on three separate occasions – first with tap water by the patient, secondly in the accident and emergency department of one of several large local general hospitals to which the patient was first referred, and finally at the Western Ophthalmic Hospital. Irrigation at the referring hospital was usually with normal saline, and a universal buffer solution (potassium dihydrogen orthophosphate 70 g, sodium phosphate *BP* 180 g, distilled water to 1 litre) was used in all cases at the Western Ophthalmic Hospital.

Conjunctival sac pH. Universal indicator paper was used to test the conjunctival sac pH on the patient's arrival and was alkaline in 46 cases (51%), with a pH range of 7·0–9·0, neutral in four cases (4%), acidic in one case (1%), and was unrecorded in the remaining 40 cases (44%) (total 91 eyes).

Initial classification of severity of injuries. The severity of injury was assessed according to Roper-Hall's[13,14] grading system. The majority of injuries (73% were minimal (grade I). However, in 25% patients (16/64) or 19% of injured eyes (17/91) there was total loss of corneal epithelium with varying degrees of limbal ischaemia. There was 180–360° limbal ischaemia in nine eyes (grade 4), 90–180° in two eyes (grade 3), and <90° in six eyes (grade 2) (Table I).

The degree of limbal ischaemia was often difficult to assess at first owing to gross chemosis and intraconjunctival and subconjunctival haemorrhage. Marked corneal stromal oedema was seen in all grade 3 and 4 injuries. A dilated pupil with large amounts of iris derived pigment on the corneal endothelium was indicative of very severe injury. Acute anterior capsular lens opacities, resembling Glaukomflecken were noted within two days of injury in the nine most severely injured eyes, reflecting chemical damage to the anterior lens capsule. A hypopyon was seen on the second day after injury in four eyes.

IOP. A raised intraocular pressure (IOP) was noted in four eyes at presentation, in patients who all had severe injuries. (Actual IOP values were 40, 28, and 28 mmHg on day 1, and 28 mmHg on day 3 by Goldmann applanation tonometry.) Measurement of ocular pressure at presentation was often difficult owing to lid swelling and profuse watering and discomfort. This may explain why there were few early recordings of ocular pressure in the more severe injuries, despite evidence that such measurement is important.[15,16] The incidence of raised IOP in grade 3 and 4 injuries is thus likely to have been an underestimate.

TABLE I *Grading of severity of injuries at presentation*

Grade	*No of patients (n=64)*	*Eyes affected (n=91)*
1	48 (73%)	74 (81%)
2	6 (9%)	6 (7%)
3	2 (3%)	2 (2%)
4	8 (15%)	9 (10%)

One patient with severe bilateral injuries had persistent ocular hypotony, first noted on day 4 and most likely due to ciliary body damage. Only one patient developed late secondary glaucoma. However, since corneal vascularisation and scarring caused problems with applanation tonometry, this may again be an underestimate.

ADMISSION POLICY

Thirty one patients (48%) were admitted to hospital and 33 (52%) treated as outpatients according to the severity of eye injury. The inpatient stay was an average 3·3 days, range 1–14 days. Outpatient visits were an average of 5·3 attendances per patient, with a range of 1–50 outpatient attendances. The period of outpatient follow-up ranged from one day to 4 years.

TREATMENT

The patients were reviewed regularly as dictated by the severity of their injuries, though at no fixed time intervals. They were discharged after the first visit if the injury was very mild – for example, superficial punctate corneal erosions or mild conjunctival epithelial loss only.

Grade 1. The mildest injuries with punctate corneal epithelial erosions or with minimal corneal epithelial loss were treated with topical antibiotics (chloramphenicol) and mydriatics (cyclopentolate) alone.

Grades 2–4. All patients with more serious injuries (grades 2–4) were treated with ascorbate drops,[17–19] initially hourly then usually reducing to two-hourly after three days. Ascorbate drops were continued until the corneal epithelium had healed. All patients were also given chloramphenicol drops initially two-hourly, and a mydriatic, usually atropine 1% drops in the more severe injuries, and cyclopentolate 1% in milder injuries. Topical steroid drops were given for all grade 2–4 injuries, usually dexamethasone hourly initially for the more severe injuries. Topical steroid treatment was continued for several weeks in the more severe cases, and no attempt was made to reduce or stop steroid treatment after one week. Despite this policy there was only one case of corneal perforation.

No patients were treated with autohaemotherapy, paracentesis, or other emergency surgical procedures which have been suggested as means of limiting progressive chemical damage. The patients were under the care of several different doctors, and there was no strict treatment protocol. However, management was essentially the same in all cases as outlined above, with only minor variations in treatment.

Cost of treatment. The approximate total cost of treating all 64 patients based on an inpatient figure of £200/day and outpatient figure of £35/visit at 1988 prices was £500 per patient.

CLINICAL COURSE AND OUTCOME

Visual. The corneal epithelium rapidly healed in one to three days in the 47 patients (73%) with grade 1 injuries. Twenty seven of these patients were reviewed on one occasion at periods ranging from four to 18 months after the original injury. None had any residual eye symptoms, though two patients had mild superficial inferior corneal scarring.

TABLE II *Visual outcome in 16 most severely injured patients (with total corneal epithelial loss)*

Patient	*Acuity*	*Follow-up (months)*	*Outcome*
Grade 4 (severe)			
1	CF	36 months	LO, penetrating graft, recurrent epithelial breakdown
2	CF	27	LO, heavily vascularised cornea, ptosis
3	HM	16	LO, secondary glaucoma, ptosis
4	PL, PL	18	LOs, persistent corneal epithelial defects, severe hypotony, depression
5	PL	12	LO, depression
6	PL	12	LO, *Staph aureus* keratitis at 4 weeks
7	HM	12	LO, Hypopyon on day 1, bacterial keratitis at 32 days, eviscerated at 5 weeks
8	HM	1 day*	Took own discharge from hospital, hysterical
Grade 3			
9	6/12	12	LO, 2 mm ptosis, superior pannus down to visual axis
10	6/7·5	8	Superior pannus
Grade 2			
11	6/5	12	No sequelae
12	6/9	12	Inferior pannus and corneal scarring
13	6/12	1 day*	Foreign visitor, returned home
14	6/4	8	Inferior corneal scarring
15	6/7·5	12 days*	Lost to follow-up
16	6/4	15	Minimal inferior corneal scarring

PL=perception of light. HM=hand movements. CF=counting fingers. LO=acute lens opacities present *Short follow-up.

Three out of six patients with grade 2 injuries had superficial inferior corneal scarring but were asymptomatic after a few weeks, with subjectively normal vision at follow-up on average 12 months later (see Table II). However, two of the six patients were lost to follow-up at one and 12 days. In one West Indian patient with a grade 2 injury ischaemic damage to the inferior limbus and presumably to bulbar conjunctival melanocytes caused local loss of conjunctival racial melanosis adjacent to the limbus. The two patients (3%) with grade 3 injuries suffered a moderate permanent reduction of vision with marked corneal vascularisation. The eight most severely injured patients (15%) had devastating grade 4 injuries, with gross corneal scarring and vascularisation, and permanently severely reduced vision, which was bilateral in one case (Fig 3).

Delayed epithelial healing. In grade 1 injuries the corneal epithelium was usually intact after four days even when there was subtotal corneal epithelial loss. Corneal epithelial healing was similarly only slightly retarded in grade 2 injuries. However, impaired corneal epithelial healing was a frequent problem in grades 3 and 4 injuries. The corneal epithelium eventually covered the denuded and damaged cornea after 11–53 days in six of these patients, In five eyes of four patients persistent epithelial defects were associated with stromal lysis and thinning.

Infective keratitis. There were two cases of infective keratitis, both caused by *Staphylococcus aureus*. Both occurred four weeks after the chemical injury in patients with persistent corneal epithelial defects and progressed to perforation of the globe in one case. This case occurred seven days after the insertion of a 'bandage' soft contact lens which had been

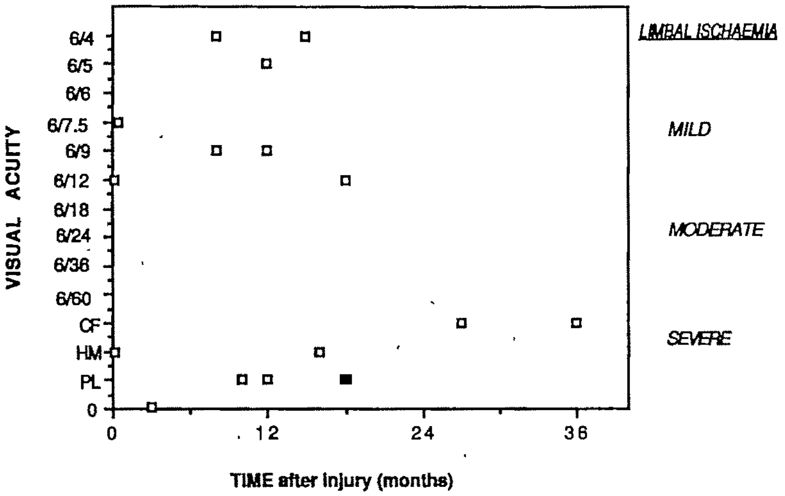


Figure 3: Visual acuity follow-up on 17 eyes with total corneal epithelial loss. ■ Represents both eyes of one patient.

inserted in order to encourage corneal re-epithelialisation.

Corneal graft. Only one of the 64 patients underwent corneal grafting, performed at 20 months after injury. After an initial reasonable visual result (6/18 corrected vision) the continuous 10/0 nylon corneal suture became loose and had to be removed. Removal of graft sutures led to recurrent corneal epithelial breakdown, necessitating continuous wear of a bandage soft contact lens and a disappointing visual result.

Lid complications and symblepharon. A mild 1–2 mm ptosis was seen in six patients with severe injuries, which persisted for six months or more. In cases with ptosis significant upper tarsal conjunctival scarring was present, with slight inward buckling of the tarsal plate in three patients. However, there were no cases of actual upper lid entropion.

Surprisingly, we saw no cases of significant symblepharon among the 64 patients. This may be a reflection of both the severity of burn and also possibly the types of chemicals that were used for assault, since symblepharon is well known to be a common complication of severe lime burns.

Psychological problems. These were common in the aftermath of injury. Depression occurred often in the more severely injured patients, where the final result was frequently an unsightly, red, uncomfortable, and almost blind eye. One patient had severe bilateral injuries and is now registered as blind. He has been severely depressed and has tried to commit suicide on several occasions.

Discussion

Violent crime in London rose by a quarter between 1986 and 1987.[20] The incidence of chemical eye injuries[11 12] due to assault has risen in parallel, though the sudden upsurge seen in 1987–8 seems to have temporarily abated.

The only other recently published large series of ocular alkali burns resulting mainly from assault was a retrospective study from the USA by Klein and Lobes in 1984,[21] which contrasts sharply with the present series. Of the 52 patients whose notes contained sufficient information, assault was the cause in at least 35 cases. The assailants were all women where described; 22% of assaults took place in the home, and 44% of the victims were chronic alcoholics. There was a high proportion of very severe burns, with 39% of 100 eyes classified as very severely damaged under the Hughes classification, compared with only 12% (grades 3 and 4 combined) in the current series. In the American series 58% of eyes had a final visual acuity of less than 20/200 and a high perforation rate of 13 out of 100 eyes; 67% received topical steroids, though none were treated with ascorbate or citrate drops.[17] The very high rate of symblepharon (29%), and secondary glaucoma (18%) in that series is a further indication that patients were more severely injured.

CONCLUSIONS

The nine most severely injured patients in the present series fared badly, though only one eye became perforated. The low perforation rate is no doubt a reflection of milder injury and it is not possible to speculate usefully on whether the additional use of topical ascorbate may have in any way contributed to the better outcome. The dismal visual results after severe alkali burns of the eye have been previously emphasised by Pfister[8]: 'The best result that can be obtained in an eye after a severe alkali burn is a totally vascularised and scarred cornea that has not undergone ulceration and in which glaucoma has not developed.'

The most important conclusions to be drawn from this study are that severe chemical burns of the eye still fare badly despite the introduction of ascorbate and steroid treatment, and that such patients are expensive to treat. Effort should therefore be directed towards the prevention of such injuries in the future. Suggested means by which this could be achieved are:

(1) *Identification* of the chemical weapons used in assault cases.

(2) *Limiting availability.* The banning of over the counter sales of noxious substances is a possible option, as has been previously suggested.[21] The continued sale of ammonia to persons under 18 demands particular consideration. Safer but no less efficacious household cleaning agents are widely available.

(3) *Education.* The extreme urgency of effective and prolonged irrigation with tapwater after any chemical contact with the eye should be stressed to the public, ambulance, first-aid, and accident and emergency staff. All medical, nursing, and paramedical staff should receive detailed instruction on irrigation technique, including eversion of the eyelids.[22]

(4) *Treatment.* Further research is needed into means by which the poor visual prognosis for severe chemical eye injuries can be improved.

1 Duke-Elder S *A system of ophthalmology* London: Kimpton, 1972, 14 (2) 1011–207.
2 Grant WM *Toxicology of the eye*. Springfield: Thomas, 1986. 3rd ed.
3 Wright P the chemically injured eye. *Trans Ophthalmol Soc UK* 1982; 102: 85–7.
4 Hughes WF Jr. Alkali burns of the eye: I Review of the literature and summary of present knowledge. *Arch Ophthalmol* 1946; 35: 423–49.

5 Hughes WF Jr. Alkali burns of the eye· II. Clinical and pathologic course. *Arch Ophthalmol* 1946, **36**: 189–214.

6 McCulley JP. Chemical Injuries. In: Smolin G, Thoft RA, eds. *The cornea scientific foundations and clinical practice*. Boston, Toronto· Little, Brown, 1983; chapter 14: 422–35.

7 Nelson JD, Kopietz LA. Chemical injuries to the eyes. emergency, intermediate, and long term care. *Postgrad Med* 1987; 81: 62–75.

8 Pfister RR. Chemical injuries of the eye. *Ophthalmology* 1983; **90** 1246–53.

9 Pfister RR, Koski J. Alkali burns of the eye: pathophysiology and treatment. *South Med J* 1982, 75: 417–22

10 Pereleux A. Chemical burns of the eye. *Bull Soc Belge Ophthalmol* 1986; **217**: 35–43.

11 Beare JD, Wilson RS, Marsh RJ Ammonia burns of the eye: an old weapon in new hands. *Br Med J* 1988; **296**: 590.

12 Morgan SJ. Chemical burns of the eye· causes and management. *Br J Ophthalmol* 1987; 71; 854–7

13 Roper-Hall MJ. Thermal and chemical burns *Trans Ophthalmol Soc UK* 1965; 85: 631–46.

14 Eagling EM, Roper-Hall MJ. *Eye Injuries· an illustrated guide*. London. Butterworths, 1986.

15 Paterson CA, Pfister RR Intraocular pressure changes after alkali burns. *Arch Ophthalmol* 1974; **91**: 211–8

16 Chiang TS, Moorman LR, Thomas RP. Ocular hypertensive response following acid and alkali burns in rabbits. *Invest Ophthalmol Vis Sci* 1971, **10**: 270–3

17 Pfister RR, Paterson CA, Hayes SA Topical ascorbate decreases the incidence of corneal ulceration in alkali burned corneas. *Invest Ophthalmol Vis Sci* 1978; **17**: 1019–24

18 Pfister RR, Paterson CA Ascorbic acid in the treatment of alkali burns of the eye *Ophthalmology* 1980; **87**: 1050–7.

19 Levinson RA, Paterson CA, Pfister RR. Ascorbic acid prevents corneal ulceration and perforation following experimental alkali burns. *Invest Ophthalmol Vis Sci* 1976; **15**: 986–93.

20 Kirby T. Crime being forced onto the streets. *Independent* 16 December 1988: 4 (cols 1–5)

21 Klein R, Lobes LA. Ocular alkali burns in a large urban area. *Ann Ophthalmol* 1976; 8: 1185–9

22 Beare JD Management of chemical burns of the eye In: Murray V, ed. *Major chemical disasters – medical aspects of management* London: Royal Society of Medicine Services International Congress and Symposium Series No. 155, 1990· 151–61 (in press)

For those patients who should avoid taking nonselective ocular beta blockers...

“Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”[1]

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

A bright outlook for glaucoma patients

For effective control of IOP minimising the risks associated with nonselective beta-blockade [2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only β_1 selective ocular beta blocker

SELECTIVE β_1 BETA-BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased cornea sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have bee reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depressive neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies have not demonstrated any specific hazard there are no adequate and well-controlled studies in pregnan women. Because animal studies are not always predictive of human response this drug should be use during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known whethe Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is administere to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed fro the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml droptainer **PRODUCT LICENC HOLDER AND NUMBER:** Alcon Laboratories U.K. 0649/0097. DATE OF PREPARATION JANUARY 199

Further information is available on request

Alcon

SPECIALISTS IN EYE CARE

Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

REFERENCES:
1. Jones FL, Ekberg NL. Letter N Eng J Med 1979; **301**: 270
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62
3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184

British Journal of Ophthalmology, 1990, 74, 519–522

Staining of the conjunctiva and conjunctival tear film

Joseph A Eliason, David M Maurice

Department of Ophthalmology, Stanford University Medical Center, Stanford, USA
J A Eliason
D M Maurice

Correspondence to:
D Maurice, Department of Ophthalmology A157, Stanford University Medical Center, Stanford, CA 94305, USA

Accepted for publication
15 March 1990

Abstract

Both the distribution of tear fluid over the conjunctiva and any injury to the conjunctival epithelium can be made visible by instilling a fluorescent solution into the eye and observing with an appropriate combination of excitation and barrier filters. Sulphorhodamine B, which has an orange fluorescence that can be separated from the green natural fluorescence of the ocular tissues, gives a greater contrast than fluorescein. The tear film is seen to cover the surface of the conjunctiva and to be concentrated in its folds. Small circular areas of thin tear film appear transiently in the neighbourhood of the limbus after a blink. Occasional cells stain on the normal conjunctiva, particularly in the interpalpebral area. The density of the staining increases in dry eye conditions. Conjunctival trauma is sensitively revealed by the method, and its healing can be followed. Hard contact lenses are seen to traumatise continually the inferior limbal conjunctiva in symptomless wearers.

The instillation of a drop of fluorescein is a common method of detecting injury to the corneal epithelium. Before damaged cells are revealed by the stain, the precorneal tear film is coloured by the dye, and it is possible to examine it for normal variations in uniformity or for the appearance of dark patches when the layer breaks up. The conjunctival cells and the preconjunctival tear film may be of equal physiological and pathological interest to that of the corneal epithelium, but no equivalent method of staining them has been available. Rose Bengal is employed as a stain for conjunctival damage, but it provides poor contrast as usually applied, and is uncomfortable when instilled in the eye.

There are three reasons why staining with fluorescein has not been found valuable over the conjunctival surface:

(1) The use of an inefficient optical filter system. Generally, a cobalt filter has been placed in front of the slit-lamp light and the eye has been observed under the microscope without the intervention of a barrier filter. This is adequate for the observation over the dark background of the cornea, but the scattering of the incident blue light by the sclera hides the weaker fluorescent light emitted by the dye.

(2) The background fluorescence of the tissue. Even with an efficient pair of excitation and barrier filters the blue incident light will excite a greenish fluorescence in the conjunctiva and sclera, which is seen as a general glow that reduces the contrast of the fluorescein.

(3) Penetration of fluorescein. Because of the slight lipid solubility of the dye, it can stain the conjunctiva tissue appreciably, and this further reduces the contrast between the surface and the background.

It was thought possible that problem (3) could be overcome by the use of a more hydrophilic dye such as carboxyfluorescein, but it was decided to evade problem (2) as well by using the fluorophore, sulphorhodamine B, which is not only very hydrophilic but can be excited by wavelengths too long to lead to visible fluorescence in the tissues. When observed with an appropriate pair of colour filters, it allowed both the tear film and devitalised conjunctival cells to be readily observed with high contrast against the tissue background.

The purpose of this report is to emphasise the advantages of an appropriate pair of colour filters when fluorescent dyes are used to examine the conjunctival surface, and to illustrate the additional benefit of using a dye with larger wavelength fluorescent characteristics than fluorescein. In addition, we note some hitherto undescribed physiological and anatomical properties of the conjunctival tear film and survey some clinical conditions in which the technique might prove to have value. (These observations have already been briefly noted in the abstracts of the First Meeting of the International Society of Dacriology, Budapest 1987, and ARVO 1988.)

Materials and methods

Sulphorhodamine B (molecular weight 559) is similar in chemical structure and properties to fluorescein but is less lipid soluble, with an octanol/water partition coefficient of 0·0033 compared with 0·61 for fluorescein.[1] Its fluorescence is orange and is most readily excited by green light, the peak absorption and emission wavelengths being 556 and 572 nm. It is usually supplied as an acid and must be dissolved in alkali, being soluble to the extent of about 20 g/l at pH 7. The toxicity of the compound appears to be very low. Doses of up to 1 g/kg could be injected intraperitoneally in the mouse without causing death, and 50 μl of the saturated solution injected into the stroma of a rabbit cornea had as little effect as an equal volume of saline.

The subjects were patients, residents, and staff of the ophthalmology clinic. Informed consent was obtained after the nature of the procedure had been fully explained A 0·5% solution of the dye at pH 7, made 300 mM with sucrose, was used to stain the tear film and a small drop was applied to the tarsal conjunctiva with a wooden applicator. The solution did not cause discomfort in the eye of any volunteer or patient. It is not important, however, to adhere exactly to this dye formulation.

The eye was observed with a Haag-Streit 900 slit-lamp using a broad patch of illumination. A band-pass interference filter of 520–550 nm, such as is used as a barrier filter for fluorescein, was inserted in the illuminating light path, and gelatin absorption filters (Kodak No 22) transmitting 100% of the light at 600 nm were placed in the eyepieces. This combination of filters passes less than 0·01% of light at the cross-over point of their absorption curves, around 570 nm. Photographs were taken with a Zeiss photoflash slit-lamp on 1600 ASA colour film with the same combination of filters. Black-and-white film of similar speed can also be used.

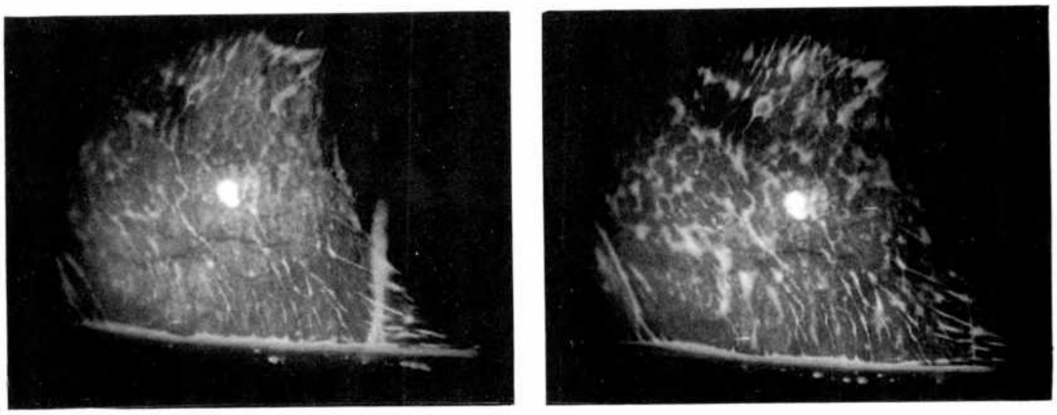


Figure 1A

Figure 1B

Figure 1 Staining of tear film with sulphorhodamine B in a normal subject. ((A) Pattern over conjunctiva immediately after a blink. (B) Same area of conjunctiva a few seconds later. Note the enhancement of lines and patches with time.

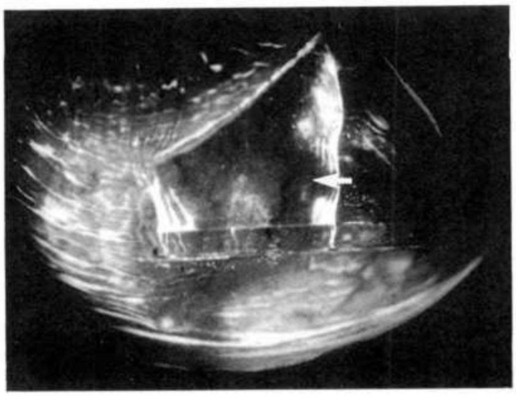


Figure 2 Disappearance of conjunctival pattern with gentle pressure from a transparent plastic plate (arrow).

Results

NORMAL TEAR FILM

In the absence of the dye the tissues of the eye appeared black through the microscope, making focusing on the ocular surface difficult. Pinguecula gave rise to a natural fluorescence which was absent in normal sclera or cornea.

After the dye was instilled the precorneal tear film and the lacrimal strips shone as brilliantly as they do with fluorescein under blue illumination. Furthermore, the conjunctiva was seen, in the first moments after instillation, to be covered with a more or less uniform tear film. Shortly thereafter a system of lines and patches appeared which became more prominent during the first seconds immediately after opening the eye, while the fluorescence of the tear film covering the area between them became weaker (Figs 1A, B). These seem to be a result of accumulations of fluid rather than tissue staining, since they disappeared after thorough flushing with saline or on pressing the conjunctiva under a clear plastic plate (Fig 2). Many features of the patterns of the lines remained constant over a long period, and they almost certainly correspond to folds in the conjunctiva (Figs 3A, B). The wider patches may represent layers of mucus or broad depressions in the conjunctival surface. The thickness of the mucus layer on the conjunctiva has been reported to vary over the surface.[2]

Some transient phenomena occur after a blink. The tear film over the entire cornea and conjunctiva appeared to flow upwards immediately after the opening of the eye. This movement lasted for about 3 seconds. Often circular dark patches about 1 mm in diameter were observed in the tear film over the conjunctiva and cornea, most frequently near the limbus (Fig 4). They appeared immediately after a blink, flowed upward with the tear film, and vanished in a second or two by constricting to smaller diameters. The origin of these spots has not been examined, but it seems most likely that they would correspond to an area where the aqueous layer is thinner rather than where it is diluted.

CONJUNCTIVAL STAINING

If the dye was removed from the tear film by thorough flushing with saline, or if it was allowed time to be washed out in the normal tear secretions, the background that remained was either dark or showed a faint orange glow from dye that

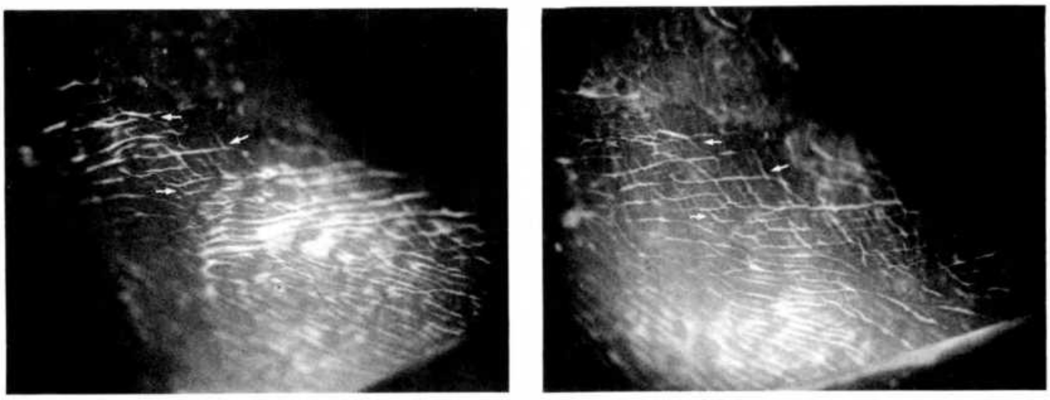


Figure 3A

Figure 3B

Figure 3 Staining with sulphorhodamine B in a normal subject. (A) Pattern of conjunctival lines. (B) Same area of conjunctiva after an interval of a year. Arrows indicate some of the similarities.

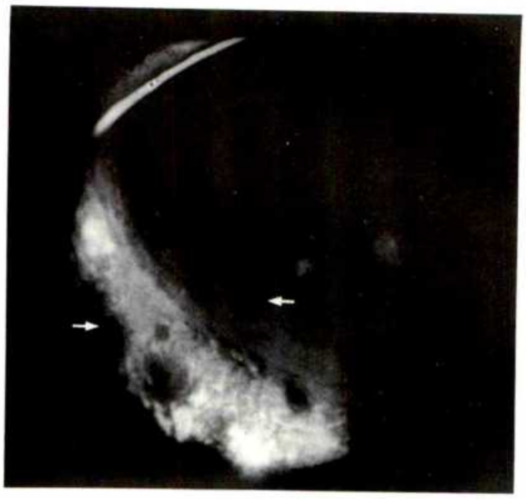


Figure 4 Dark patches (arrows) noticed here on both sides of the limbus, which were observed to move with the tear film.

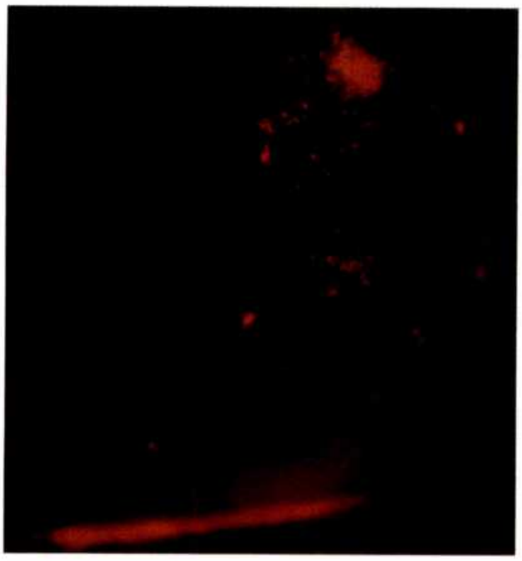


Figure 5 Conjunctival staining along the limbus in the interpalpebral zone in a normal eye. Also note prominent staining of the tear meniscus along the lower lid margin.

had penetrated into the tissue. In the normal eye bright staining spots were seen, occasionally on the cornea but more frequently over the conjunctiva, particularly the interpalpebral zone (Fig 5). Sometimes small patches of staining were observed. The spots retained sharp outlines and could be observed for hours, though usually they disappeared by the next day and were not constant on restaining the tissue. They probably correspond to individual epithelial cells that are either damaged or in a permeable condition before desquamation. Patches of staining also appeared where the tarsal or bulbar conjunctiva had been touched by the applicator. In one eye a brilliantly staining zone of conjunctival damage was created by the rotation of the wooden end of a sterile Q-tip, and its recovery healing could be followed by restaining at intervals (Fig 6A, B). In this case a portion of the initially applied stain was still present after 24 hours.

In each one of four symptomless gas permeable contact-lens wearers notable staining in the form of a confluent band superimposed on a fine line was found on the conjunctival side of the inferior limbus (Fig 7).

COMPARISON WITH FLUORESCEIN AND ROSE BENGAL

In 12 patients with Sjøgren's syndrome conjunctival staining with sulphorhodamine B was found to be more evident than that detected with fluorescein (Figs 8A, B). Corneal staining was similar with both dyes. This subjective impression that sulphorhodamine B staining was more sensitive than that with the other dyes was given a quantitative test. Observations were carried out on 14 eyes of seven normal subjects with 1% fluorescein, 0·5% rose Bengal, and 0·5% sulphorhodamine B. The blue and green excitation filters provided with the Haag-Streit 900 slit-lamp were used to observe the fluorescein and rose Bengal dyes, and the excitation and barrier filters described above were used for the sulphorhodamine. While this arrangement should provide better contrast for viewing the sulphorhodamine, the recognition of punctate staining spots over the conjunctiva with fluorescein was judged similar with or without the use of a barrier filter. Punctate staining was quantitated by the grading scheme described by van Bijsterveld[3] using four areas: cornea, and nasal, temporal and inferior conjunctiva. Each area was graded on a 0 to 3 scale: 0=no punctate staining; 1=small (that is, readily countable) number of punctate staining spots; 2=numerous (that is, not countable) spots; and 3=staining that was confluent or approaching confluence. The scores for each eye were added to reach a total of 0 to 12.

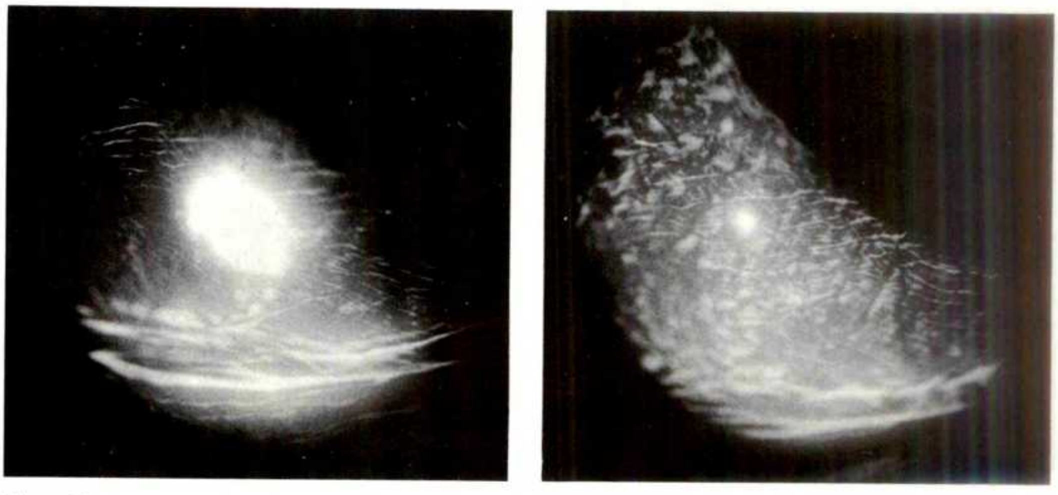


Figure 6: Sulphorhodamine B staining of the conjunctiva in a normal subject. (A) Area of conjunctival damage stained immediately after its production. (B) Restained 24 hours later, showing almost complete healing of the defect.

Figure 6A

Figure 6B

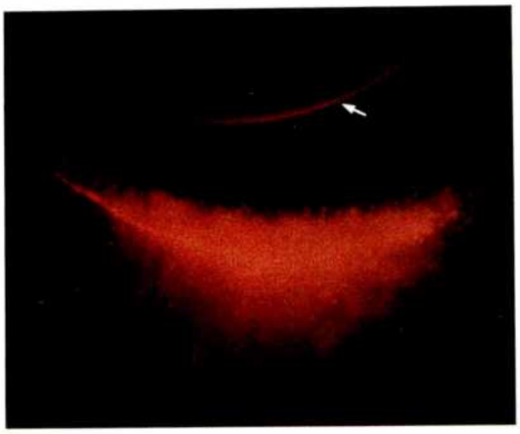


Figure 7 Bright band of staining along the inferior limbus in a rigid contact lens wearer. Also note faint edge of lens riding on the cornea (arrow).

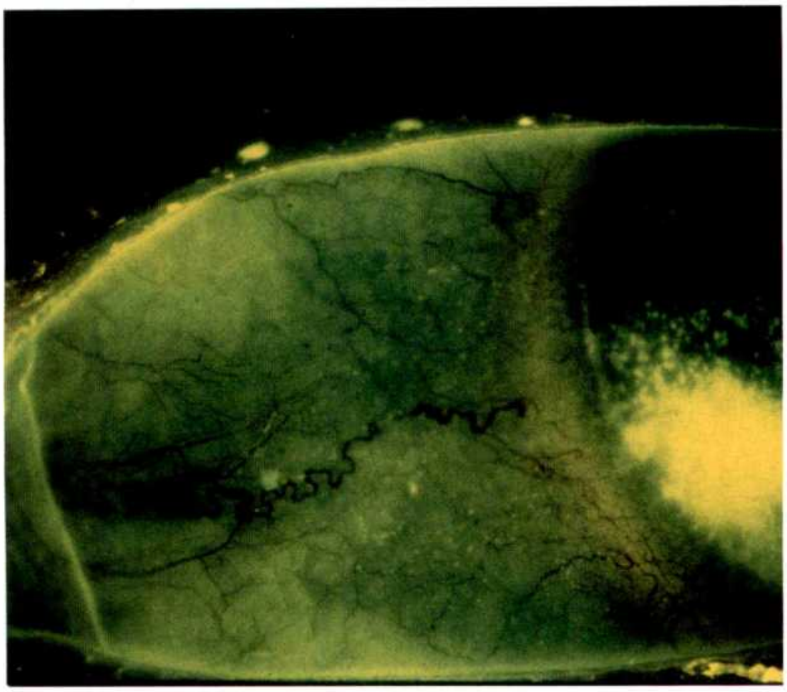


Figure 8A

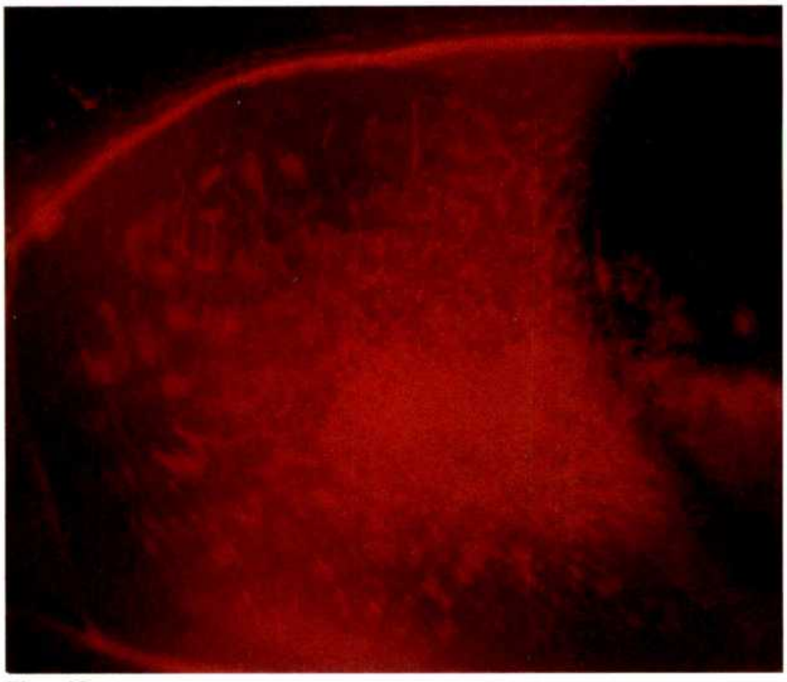


Figure 8B

Figure 8 (A) Conjunctival staining in a patient with primary Sjøgren's syndrome by means of fluorescein photographed with excitation and barrier filters. (B) Same location with sulphorhodamine B. Note large area of confluent staining in the interpalpebral fissure area not evident with fluorescein and absence of distracting blood vessels.

Mean scores for the dyes were : fluorescein 1·0, rose Bengal 1·2, and sulphorhodamine 2·7. Evaluated with the non-parametric Wilcoxon signed rank test, the difference between the fluorescein and rose Bengal scores was significant only at the 5% level, while the differences between either fluorescein or rose Bengal and sulphorhodamine were significant at the 1% level.

Discussion

Fluorescein staining of the cornea or the precorneal tear film can be readily observed under a white light or with a cobalt filter, but the dye is scarcely visible on the conjunctival surface. The use of an efficient pair of excitation and barrier filters leads to a considerable increase in contrast of the dye and allows conjunctival lesions to be identified. However, the blood vessels of the conjunctiva show up as a system of black lines which is disturbing, and background fluorescence is appreciably greater following washout of the dye, so that contrast is poorer and the detection of small lesions is difficult. The lines are not visible when sulphorhodamine B replaces fluorescein, and the contrast over the conjunctiva is much improved. The colouration with rose Bengal observed in white light seemed to be the weakest of all, but it was more visible when excited with green light.

From our comparison of the three dyes we consider that sulphorhodamine B is the most capable of revealing subtle surface abnormalities. Although fluorescein under our operating conditions resulted in an image easier to photograph, this is not an important consideration for visual observations. Punctate staining with sulphorhodamine B could be detected in all eyes considered normal and asymptomatic which we examined. An increase in the sensitivity of detection of ocular surface abnormalities may result in new diagnostic insights. Thus the evidence of limbal epithelial damage in asymptomatic contact lens wearers we believe to be original. It is probable that this considerable epithelial injury occurs when the edge of the lens is driven down on to the limbus on blinking. Damage to the important repopulating limbal epithelial cells may explain the poor surface healing behaviour observed in long-term lens wearers.

Further experience is required to determine whether this increase in sensitivity will lead to an improvement in diagnosis sufficient to warrant the general use of sulphorhodamine B. An important prerequisite is a method of readily inserting colour filters in the lamp and the microscope optical pathways. The system we have employed is too slow and awkward for regular use.

This work was supported by EY 04863 and Research to Prevent Blindness, Inc.

1 Araie M, Maurice D. The rate of diffusion of fluorophores through the corneal epithelium and stroma. *Exp Eye Res* 1987; **44:** 73–87.

2 Nichols BA, Chiappino ML, Dawson CR. Demonstration of the mucous layer of the tear films by electron microscopy. *Invest Ophthalmol Vis Sci* 1985; **26:** 464–73.

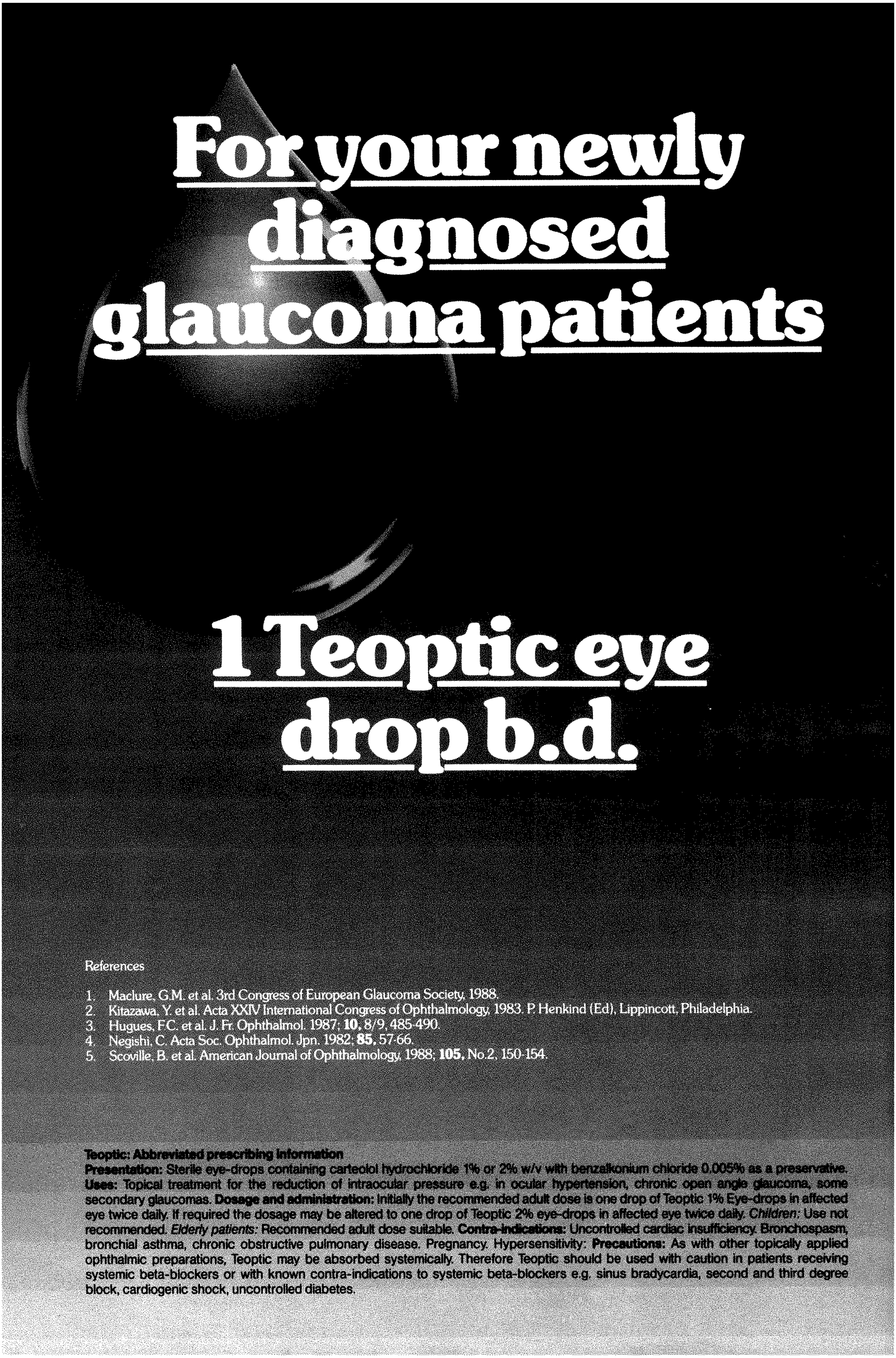
3 van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol* 1969; **82:** 10–4.

Pred·Forte™
prednisolone acetate 1.0%
POWER
in ocular inflammation
Provides excellent penetration[1]
for the treatment of iritis, uveitis
and other steroid responsive inflammations
of the anterior segment.

Pred Forte™ Prescribing Information
Presentation: White, microfine, sterile ophthalmic suspension containing 1.0% prednisolone acetate and preserved with 0.006% benzalkonium chloride and 0.0127% disodium edetate. **Uses**: For short term treatment of steroid-responsive inflammatory conditions of the eye, after excluding the presence of viral, fungal and bacterial pathogens. **Dosage and Administration**: One to two drops instilled into the conjunctival sac two to four times daily. During the initial 24-48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contra-Indications, warnings, etc**: **Contra-indications** Acute untreated purulent ocular infections. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Fungal diseases of the eye. Ocular tuberculosis. Sensitivity to any component of the formulation. **Warnings** Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. Pred Forte contains no antimicrobial agent. If infection is present, appropriate measures must be taken to counteract the infective organisms. Fungal infections of the cornea have been reported coincidentally with long-term steroid application, and fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal or scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. Pred Forte contains benzalkonium chloride as a preservative and should not be used in patients continuing to wear hydrophilic (soft) contact lenses. **Use in pregnancy** The safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. **Precautions** Patients with a history of herpes simplex keratitis should be treated with caution. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent, mandatory, slit lamp microscopy. Use of topical corticosteroids may cause an increase in intraocular pressure in certain individuals. This may result in damage to the optic nerve with resultant defects in visual fields. It is advisable that intraocular pressure be checked frequently during treatment with Pred Forte. **Side effects** Possible adverse reactions include: increased intraocular pressure; secondary ocular infections from fungi or viruses liberated from ocular tissues; perforation of the globe when used in conditions where there is a thinning of the cornea or sclera. Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids. Extensive topical use of corticosteroids may lead to systemic side effects. **Overdosage** There is no clinical experience of overdosage. Acute overdosage is unlikely to occur via the ophthalmic route. **Pharmaceutical Precautions**: Protect from freezing. Shake the bottle well before use. **Legal Category**: POM. **Package Quantities**: Plastic dropper bottle containing 5ml or 10ml. **Basic NHS cost** (as at March 1988): 5ml – £1.55; 10ml – £3.09. **Further information**: Nil. **Product Licence number**: 0426/0051. **Date of preparation**: February 1988. **Reference** 1. Leibowitz HM, Berrospi AR, Kupferman A. Am J of Ophthalmology 1977; **83**(3): 402-406.

ALLERGAN PHARMACEUTICALS™
· OPHTHALMIC STEROIDS ·
GOING FROM STRENGTH TO STRENGTH

Full prescribing information is available on request. Allergan Limited, High Wycombe, Bucks. HP12 3SH. ™denotes trademark.



For your newly diagnosed glaucoma patients

1 Teoptic eye drop b.d.

References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10,** 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85,** 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105,** No.2, 150-154.

Teoptic: Abbreviated prescribing information

Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity: **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

- **Effectively lowers IOP**[1]
- **Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol** *[2,3]
- **Has a prolonged therapeutic effect**[4] **thus offering flexible b.d. dosage regimen**
- **Well tolerated with few local side-effects**[5]
- **Low concentration of benzalkonium chloride in a buffered solution.**

*** Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.**

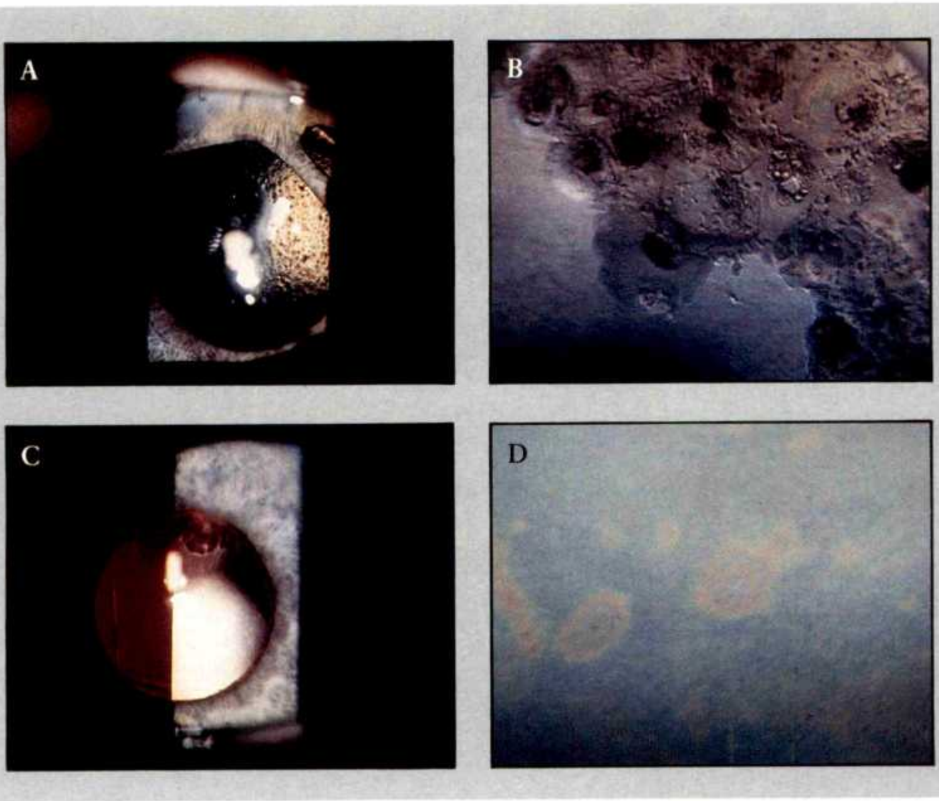
Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.

Teoptic is under licence from Otsuka, Japan.

Further information is available on request to the above address.

Comparison between Heparin surface modified IOLs and normal IOLs in the same patient.



This female has a history of longstanding diabetes and glaucoma.

A. Slit lamp
B. Specular microscopy

Right eye — NORMAL PMMA LENS

- 11 months post-operatively
- Confluent giant cells can b seen clearly on both slides

C. Slit lamp
D. Specular microscopy

Left eye — HEPARIN SURFACE MODIFIED LENS

- 6 months post-operatively
- No giant cells
- Newton's rings seen clearly

A clear case for Heparin surface modified IOLs.

Pharmacia Limited,
Ophthalmics Division, Pharmacia House, Midsummer Boulevard, Milton Keynes MK9 3HP.
Telephone: (0908) 661101. Telex: 826778. Fax: (0908) 690091

Pharmac

British Journal of Ophthalmology, 1990, 74, 523–525

Acute closed-angle glaucoma and Nd-YAG laser iridotomy

D C Saunders

Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WL
D C Saunders

Correspondence to:
Dr D C Saunders.

Accepted for publication 3 May 1990

Abstract

Forty-one patients presenting consecutively with acute angle closure glaucoma (AACG) were studied with a median follow-up period of eight months. Four patients presented with bilateral symptoms. Thirty-nine patients underwent Nd-YAG laser iridotomy (42 AACG eyes and 36 fellow eyes). Only 15 patients (36·6%) required simply iridotomy; the remainder required additional long term medical or surgical treatment. Longer duration of symptoms and a history of previous intermittent, spontaneously resolved AACG were more common in those requiring additional treatment. Cataract extraction with intraocular lens implantation was performed for three eyes with AACG, and this mode of treatment is discussed as a possible primary treatment. One eye with AACG suffered a second episode, and two fellow eyes developed AACG despite laser iridotomy. Possible mechanisms are discussed. Provocative testing or frequent careful observation of iridotomy patency is recommended.

This study was undertaken as an audit of a consecutive group of patients presenting with acute angle closure glaucoma (AACG) and to establish any prognostic indicators. To my knowledge only one previous study has assessed Nd-YAG laser iridotomy in AACG in more than 30 patients,[1] and none have examined a consecutive group of patients.

Patients and methods

All patients attending Manchester Royal Eye Hospital with AACG between September 1987 and March 1988 were included. The diagnosis was suspected on the basis of a history of pain and blurring of vision and confirmed by finding a raised intraocular pressure (IOP), corneal oedema, a mid-dilated pupil, and a closed iridocorneal angle. The latter was identified either by gonioscopy or direct observation of iridocorneal contact on the slit-lamp. All patients were admitted to hospital and treated medically to break the acute attack. Treatment was with intravenous and oral acetazolamide (Diamox), pilocarpine 4%, timolol, and topical steroid. Patients not responding promptly to this regimen were given intravenous mannitol. After the acute attack was controlled bilateral laser iridotomy was performed with the Lasag Neodymium YAG Series 2 Microruptor with CGI1 or Abraham contact lens, and antiglaucoma medication was stopped. Iridotomy patency was assessed by direct visualisation of the lens capsule through the iridotomy and/or by the appearance of a plume of iris pigment during treatment. If the IOP was not adequately controlled, topical antiglaucoma medication was begun again. Trabeculectomy followed if the IOP remained uncontrolled.

Results

Forty-one patients presented during the course of the study (Table 1). Four patients suffered bilateral AACG, so 45 eyes with AACG and 37 fellow eyes were studied. There was an equal distribution of left and right eyes (23 OS, 22 OD). The average age of the patients was 70·5 years (range 45–89), and 31 (75·6%) were female. All were Caucasian.

Nine patients (22%) gave a history of intermittent pain and blurring of vision or haloes, consistent with spontaneously resolved attacks of AACG. These had occurred from two weeks to 14 months prior to presentation with AACG. The duration of symptoms overall varied from 4 hours to 21 days (mean 4·7 days). Four patients with bilateral symptoms presented. Two had failed to seek medical advice for nine months following the involvement of the first eye (resulting in no perception of light), but presented promptly when the second eye became involved. One had similarly ignored the first eye for five days until the second eye was involved. One patient presented with simultaneous symptoms in both eyes.

The initial medical treatment, without mannitol, was sufficient to break the acute attack in 37 (90%) patients. Four patients required mannitol, but in only two did it break the attack.

Extracapsular cataract extraction with IOL was performed in three patients, two of whom were still in angle closure with a raised IOP at the time of surgery, which was performed as an emergency. The third underwent surgery shortly after iridotomy. He was lost to follow-up, but initially did well with a corrected visual acuity (VA) of 6/9 on no medication at three months. The other two patients did well with corrected VA 6/6 and 6/9 respectively and required no long term antiglaucoma medication. None showed signs of corneal decompensation, and there was no increased surgical morbidity.

Table 1 Acute closed-angle glaucoma treated with Nd-YAG laser iridotomy: demographic details

	Males	*Females*	*Total*
Number	10	31	41
Mean age (yr)	69·8	70·7	70·5
Mean duration of symptoms	5·5 days	4·5 days	4·7 days
Eyes			
left	4	15	19
right	5	13	18
bilateral	1	3	4
total	11	34	45

Table 2 Acute closed-angle glaucoma treated with Nd-YAG laser iridotomy: surgery required

Operation	*No.*
Trabeculectomy	8
Peripheral iridectomy	4
Extracapsular cataract extraction with IOL	3
Sector iridectomy	1

Table 3 Acute closed-angle glaucoma treated with Nd-YAG laser iridotomy: medication vs non-medication

	YAG	*ECCE+IOL*	*PI*	*Trabeculectomy*	*Total*
No treatment	15	2+1*	1	6	24+1*
Treatment	12	0	2	2	16

*Lost to follow-up, on no medication at 3 months. The underlined figures represent group A, the remainder are group B.

Table 4 Acute closed-angle glaucoma treated with Nd-YAG laser iridotomy: group A vs group B

	Group A	*Group B*
Mean duration of symptoms (days)	3·52	5·09
Median duration of symptoms (days)	2	2·5
Number with history of resolved AACG	1/18	8/22
Percentage with history of resolved AACG	5·6%	36 4%
Presenting IOP (mmHg)	55·6	53 4

None of the three had mature intumescent lenses; all had nuclear sclerosis type cataract.

Cataract surgery was performed under retrobulbar anaesthesia with 3–4 ml of bupivacaine, lignocaine, and hyaluronidase. Digital massage was used following retrobulbar anaesthesia to lower the IOP. A corneal section was used, the eye being decompressed slowly by a small puncture prior to opening the section. Standard extracapsular extraction followed, aided by a viscoelastic substance which was used to deepen the anterior chamber. The nucleus was expressed with a vectis and soft lens matter removed with an aspiration/irrigation cannula. A posterior chamber IOL was inserted in the capsular bag. No peripheral iridectomy was performed. The section was sutured with 10/0 monofilament nylon. Subconjunctival betamethasone and gentamicin followed. Postoperatively a topical steroid, an antibiotic, and a mydriatic were given for four to six weeks.

One patient was too debilitated to undergo either laser treatment or surgery and was treated with long term pilocarpine.

Thus 42 out of 45 AACG eyes and 36 out of 37 fellow eyes underwent Nd-YAG laser iridotomy; a total of 78 eyes (95%).

The Nd-YAG laser did not achieve a patent iridotomy in three patients (four eyes, two AACG and two fellow eyes), and these underwent surgical peripheral iridectomy (PI). Following surgical PI two eyes (same patient) required antiglaucoma medication. One eye suffered recurrent AACG on the first postoperative day and subsequently underwent sector iridectomy. Three (7·3%) patients suffered a second attack of AACG despite initially patent iridotomy. Two were treated with repeat Nd-YAG laser iridotomy and one required trabeculectomy. The final VA was 6/9, 6/18, and counting fingers respectively. Fifteen patients (36·5%) required no further treatment after Nd-YAG laser iridotomy, and a further nine required no treatment following surgery (total 24 patients, 58·5%).

Sixteen operations were required on 15 eyes of 14 patients. Table 2 gives details.

One patient was lost to follow-up, leaving 16 patients (39%) needing antiglaucoma medication. The lost patient was on no medication at three months. At present the IOP is not controlled in one patient. Thus 39 patients (95%) have controlled IOP.

Patients were divided into two groups: group A required no long term antiglaucoma medication and no trabeculectomy, while group B required medication and/or trabeculectomy (Table 3). Thus group B represents patients with compromised angle function, whereas group A have adequate angle function. The mean duration of symptoms of group A was 3·52 days (median 2 days), while for group B it was 5·09 days (median 2·5 days). This is a statistically significantly longer duration of symptoms in group B (rank sum test, $p<0{\cdot}01$). In group A only 1/18 (6%) had a history of previously resolved AACG, whereas 8/22 (36%) of group B had similar symptoms. The level of the IOP at presentation was not significantly different in the two groups (Table 4).

Discussion

The demographic details of the patients compare well with those found in other studies.[1,2] The one eye which suffered recurrent AACG on the first postoperative day following surgical PI had been dilated with cyclopentolate by junior staff. Lowe[3] highlighted the dangers of tropine drugs for postoperative dilatation in these circumstances and recommended 10% phenylephrine as a safer alternative.[4] Nonetheless, cases have been reported of recurrent AACG following surgical PI dilated with phenylephrine.[4,5] The mechanism of this angle closure is iris crowding into the angle rather than pupil block. Thus the tropine drugs, as powerful dilators, are more dangerous than phenylephrine, a weak dilator. This type of angle closure tends to occur in eyes with 'plateau iris' – that is, with anterior insertion of the iris, a flat iris plane, and a nearly normal axial anterior chamber depth. 'Plateau iris' has been estimated to account for 6·1% of eyes with AACG.[6] This case serves as a reminder that, with the advent of laser iridotomy, surgical PI is undertaken only rarely for the treatment of AACG, and that junior staff may be unaware of the most appropriate postoperative management.

In this study duration of symptoms prior to presentation is significant in distinguishing between those patients who will be cured by simple iridotomy and those who will require additional medication or surgery. This is in accord with the findings of Hass and Scheie[7] but at variance with those of Gray *et al.*[1] It would appear reasonable that the longer an attack lasts, the greater the risk of peripheral anterior synechiae and/or angle damage. This reinforces the need for prompt lowering of IOP.

A past history suggestive of spontaneously resolved AACG appears to be significant in distinguishing the iridotomy-only group from the additional-treatment group. This may be a true reflection of angle damage and/or peripheral anterior synechiae formation during recurrent AACG, or it may simply lead to a longer period in AACG prior to presentation, as the patient awaits the expected spontaneous resolution. In fact the nine patients presenting with a history of previous symptoms had a significantly shorter duration of symptoms for the presenting episode than those without a previous history (rank sum test, $p<0\cdot01$). Thus it would appear that a previous history of resolved AACG is independently significant in identifying those patients who are likely to need additional treatment.

The major anatomical factors of AACG eyes depend on faulty co-ordination of lens size and position in relation to axial length.[8] In a condition directly related to lens morphology and in which lens opacities may progress after the acute event (independently of intervention)[2,9] it would seem reasonable to consider cataract extraction with IOL insertion as the primary surgical treatment if significant lens opacities are already present. In this way the anterior chamber is deepened, and the angle closure relieved, without the need to perform iridotomy or iridectomy, neither of which deal with the root cause of the AACG attack. I can find reference to only four other eyes undergoing lens extraction and IOL implantation as treatment for AACG.[10] In contrast to this study, three of these had white, mature, and intumescent cataracts, while in the fourth patient AACG was precipitated by preoperative pupillary dilatation prior to routine cataract surgery. All eyes had peripheral iridectomy at the time of cataract extraction. Three eyes attained a VA of 6/12 and one of 6/9. There was no corneal decompensation or increased surgical morbidity. All eyes had a normal IOP, but all were on treatment with topical timolol long term. It would appear that cataract extraction with IOL implantation is an appropriate mode of treatment for AACG and allows early visual rehabilitation. Further evaluation of this method is needed.

Three patients suffered a second episode of AACG despite initially patent iridotomies. This mirrors the experience of Gray *et al*,[1] though in my study two fellow eyes and only one AACG eye were involved. All occurred within three weeks of laser treatment, and iridotomies were noted to be closed in all three. Transient closure of initially patent Nd-YAG laser iridotomies has been reported in 6·7% of eyes for the first three weeks following iridotomy.[11] Late failure of iridotomy by pigment epithelial proliferation was noted in 3–10% of eyes in the first three months after treatment.[11–13] Stromal healing accounted for a further 6% closure rate. Wishart and Hitchings[12] stress the importance of a large iridotomy to prevent late failure, as nine out of 10 late failures in the series had an iridotomy diameter of 150 μm or less. Wise[14] has described a low energy linear incision method of iridotomy in order to provide large iridotomies of controllable size. The method uses the Wise 103 dioptre iridotomy lens[15] and involves cutting individual iris fibres across iris tension lines.

Quigley[16] recommended provocative testing routinely after iridotomy, and Gray *et al*[1] suggested that provocative testing should be included in the early follow-up of all patients. However, Wishart and Hitchings[12] found that provocative testing did not identify those iridotomies which subsequently failed.

This study confirms that YAG laser iridotomy may be inadequate to prevent recurrent AACG but also shows that it may be inadequate as prophylaxis against AACG in previously healthy fellow eyes. Provocative testing may be of benefit in identifying eyes in which iridotomies have closed but may not be useful in identifying those which will close in future. Careful observation at frequent intervals in the first six weeks following treatment may prove as effective as provocative testing while avoiding the risk of iatrogenic AACG.

1 Gray RH, Hoare Nairne J, Ayliffe WHR Efficacy of Nd-YAG laser iridotomies in acute angle closure glaucoma *Br J Ophthalmol* 1989; 73: 182–5.
2 Krupin T, Mitchell KB, Johnson MF, Becker B The long term effects of iridectomy for primary acute angle-closure glaucoma *Am J Ophthalmol* 1978; 86: 506–9
3 Lowe RF. Primary angle-closure glaucoma Investigations after surgery for pupil block. *Am J Ophthalmol* 1964, 57: 931–8
4 Lowe RF. Primary angle-closure glaucoma investigations using 10% phenylephrine eyedrops *Am J Ophthalmol* 1965, 60: 415–9.
5 Lowe RF. Primary angle-closure glaucoma: postoperative acute glaucoma after phenylephrine eyedrops *Am J Ophthalmol* 1968, 65: 552–4
6 Godel V, Stein R, Feiler-Ofry V Angle closure glaucoma following peripheral iridectomy and mydriasis. *Am J Ophthalmol* 1968, 65: 555–60.
7 Hass J, Scheie H Peripheral iridectomy in narrow angle glaucoma *Ophthalmology* 1957; 55: 59–63
8 Lowe RF Causes of shallow anterior chamber in primary angle-closure glaucoma. *Am J Ophthalmol* 1969; 67: 87–93
9 Godel V, Regenbogen L. Cataractogenic factors in patients with primary angle-closure glaucoma after peripheral iridectomy. *Am J Ophthalmol* 1977, 83: 180–4.
10 Civerchia L, Balent A Intraocular lens implantation in acute angle closure glaucoma associated with cataract *J Am Intraocular Implant Soc* 1985, 11: 171–3
11 Naveh N, Zborowsky-Gutman L, Blumenthal M. Nd-YAG laser iridotomy in angle closure glaucoma: a preliminary study. *Br J Ophthalmol* 1987, 71: 257–61.
12 Wishart P, Hitchings R Neodymium YAG and dye laser iridotomy – a comparative study. *Trans Ophthalmol Soc UK* 1986, 105: 521–40.
13 Brazier D Neodymium YAG laser iridotomy *J R Soc Med* 1986, 79: 658–60.
14 Wise J. Low-energy linear incision neodymium YAG laser iridotomy versus linear incision argon laser iridotomy *Ophthalmology* 1987, 94: 1531–7
15 Wise J. A high efficiency laser iridotomy-sphincterotomy lens *Am J Ophthalmol* 1986; 101: 546–53
16 Quigley HA Long-term follow-up of laser iridotomy *Ophthalmology* 1981; 88: 218–24

British Journal of Ophthalmology, 1990, 74, 526–527

Influence of pupil size on measurements made with the Lens Opacity Meter 701

Michael P Clarke, James C G Pearson, Stephen A Vernon, J Colin Matthews

Academic Unit of Ophthalmology, Queen's Medical Centre, Nottingham
M P Clarke
S A Vernon

Department of Epidemiology and Community Medicine, Queen's Medical Centre, Nottingham
J C G Pearson

Department of Physics, University of Nottingham
J C Matthews

Correspondence to:
M P Clarke, FRCS

Accepted for publication
3 May 1990

Abstract

The Lens Opacity Meter 701 (Interzeag, Switzerland) is a recently developed instrument for assessing cataract. It measures the degree of scatter of a red light beam by the lens. Fifty patients prior to cataract surgery had measurements made before and after dilatation of the pupil. Inconsistent results were found at pupil diameters of less than 4 mm. It is postulated that this was due to absorption of scattered light by the iris.

The lens opacity meter 701 (LOM) (Interzeag, Switzerland) measures the back scattering of a 1·5 mm beam of 700 nm wavelength directed along the visual axis. The scattered light is detected by a photocell 27° below the incident beam. The instrument provides a quick, reproducible, numerical measurement which correlates well with slit-lamp grading.[1 2] Although it is possible to make consistent measurements through an undilated pupil, the manufacturers recommend that the pupil diameter should be at least 4 mm.[1] This limits the use of the instrument in patients with posterior synechiae and those on chronic miotic therapy. Normal values of lens scatter adjusted for age have been calculated with the Lens Opacity Meter 701.[2] Tuft *et al*[3] found a significant relationship between Lens Opacity Meter reading and Snellen acuity and age, but concluded that the LOM was more suited to the evaluation of the contribution of lens opacities to visual loss in populations rather than individuals.

We have studied lens scatter in patients with cataract prior to surgery and have assessed the influence of pupil size on the readings.

Patients and methods

Fifty patients about to undergo cataract surgery consented to be examined on the LOM. The pupil size was reduced by increasing the background illumination. In a small number of cases this was supplemented by 1% pilocarpine. The pupils were then enlarged by dimming the background light. Tropicamide 1% was then instilled to dilate the pupils further. Sequential recordings were made of lens scatter at the pupil diameters obtained.

Table 1 All data

Pupil	*Subsets*	*Values*	*df*	*Variance*	*SD*	*F*	*p*		
<4	42	94	52	43·07	6·56				
						2·17	<0·01		
≥4	50	125	75	19·79	4·45			12·97	<0·01
						5·96	<0·01		
>4	36	77	41	3·32	1·82				

Table 2 Analysis of variance of lens scatter at pupil diameters of <4 mm and >4 mm

Pupil	*Subsets*	*Values*	*df*	*Variance*	*SD*	*F*	*p*
<4	17	38	21	29·60	5·44	8·94	<0·01
>4	17	37	20	3·31	1·82		

Table 3 Analysis of variance of lens scatter at pupil diameters of <4 mm and ≥4 mm

Pupil	*Subsets*	*Values*	*df*	*Variance*	*SD*	*F*	*p*
<4	22	49	27	28·77	5·36	6·63	<0·01
≥4	22	54	32	4·34	2·08		

The pupil diameter was measured by a grating incorporated into the instrument optics.

Five measurements of lens scatter were made at each pupil diameter and a mean value and standard deviation calculated.

Results

The variation in the repeated readings of lens scatter was measured by calculating the variance (the square of the standard deviation) for each subject and pooling these variances for all subsets. The analysis was carried out for the subsets of the data defined by pupil sizes less than and greater than 4 mm respectively. Those results relating to exactly 4 mm pupil size were treated by defining the 'greater than 4 mm' subset in two ways – 'strictly greater than 4 mm', and '4 mm or more' to see what the effect of including those results on the boundary would be.

The first analysis used all of the available data, except where there was only one value in the subset, since this contributed no information on variation. Differences in variation were tested by the variance ratio (F) test[4] (Table 1).

A problem with the above analysis was that there was a lack of balance in the sets that were being compared, since some subjects contributed to one variance but not to the other, having multiple readings on only one side of the boundary. The analysis was therefore repeated, confined to those subjects who had two or more values on either side of the 4 mm division.

The first of these analyses looked at <4 mm and >4 mm, with pupil size 4 mm excluded (Table 2). The analysis was then repeated with the upper group defined as 4 mm or more (Table 3).

Discussion

Clearly there is much greater variation in the readings when the pupil size is less than 4 mm. The contrast between greater than 4 mm and

Table 4 Percentage of illuminated cylinder detected at different pupil diameters and beam offsets

Pupil diam	*Offset (mm)*												
	−1 0	*−0·9*	*−0·8*	*−0·7*	*−0 6*	*−0 5*	*−0 4*	*−0·3*	*−0·2*	*−0 1*	*−0·0*	*0 1*	*0 2*
2 00	89	91	92	92	90	88	84	78	74	68	62	56	48
2 10	91	93	94	94	93	90	86	82	76	71	65	58	52
2·20	93	95	95	96	95	92	89	85	79	74	68	61	56
2·30	94	96	96	96	95	93	91	87	82	76	71	64	59
2·40	96	97	98	97	96	95	93	89	85	80	74	68	62
2 50	96	98	98	98	97	96	94	91	87	82	77	71	65
2 60	97	98	99	98	98	97	95	93	89	84	79	75	69
2·70	98	99	99	99	99	98	96	94	91	87	83	77	71
2·80	98	99	99	99	99	98	97	95	93	90	85	80	74
2 90	99	99	99	99	99	98	98	96	94	92	87	83	78
3·00	99	99	100	99	99	99	98	97	95	93	89	85	80
3·10	99	99	100	100	99	99	98	97	96	94	91	88	83
3.20	99	99	100	100	99	99	99	98	97	95	93	89	86
3·30	99	100	100	100	100	99	99	98	97	96	94	91	88
3·40	100	100	100	100	100	99	99	99	98	97	95	93	89
3·50	100	100	100	100	100	100	99	99	99	98	96	94	91
3·60	100	100	100	100	100	100	99	99	99	98	97	95	93
3 70	100	100	100	100	100	100	99	99	99	99	98	96	94
3 80	100	100	100	100	100	100	100	99	99	99	98	97	95
3·90	100	100	100	100	100	100	100	100	99	99	98	98	96
4·00	100	100	100	100	100	100	100	100	99	99	99	98	97

4 mm or more is less distinct. There is a large difference when the full data set is used. The difference is, however, much smaller when the matched sets are examined – variances 3·31 and 4·34 respectively (F=1·31, p>0·5). This seems to suggest that those subjects where the range of pupil sizes was restricted had more variable results.

The most likely explanation for the lack of consistency in measurement of lens scatter when the pupil size is less than 4 mm is absorption of scattered light from the lens by the posterior surface of the iris. The photoreceptor for this scattered light lies at 27° below the horizontal. On the assumption of a lens thickness of at least 3 mm it is possible to calculate the proportion of the scattered light from a beam of 1·5 mm in diameter which will be detected by a receptor at 27° below the incident horizontal beam for different pupil diameters. If the whole of the illuminated cylinder is visible to the detector – that is, is not masked by the iris – the signal will correspond to 100% of its 'correct' value. If the iris masks off half of the volume of the cylinder, then the signal will correspond to only 50% of its correct value – that is, the measured lens scatter will be underestimated by 50%.

The beam is normally made to pass through the centre of the pupil. However, there may be advantage in deliberately raising it away from the centre of the iris, and such displacement will be called the offset of the beam. When the beam is raised, this will correspond to a negative offset.

Table 4 indicates the fraction of the illuminated cylinder seen by the photocell for a range of pupil diameters and a range of offsets. Although serial measurements on the same lens at pupil diameters less than 4 mm may be consistent at the same pupil diameter, these measurements will underestimate the 'true' lens scatter. This poses a difficulty if absolute thresholds of lens scatter measurement are used, as for example criteria for cataract surgery, or when serial measurements are made to assess changes in lens scatter with time. We conclude that the LOM is capable of providing a reproducible measurement of lens opacity provided the pupil diameter is >4 mm.

The authors thank the consultant ophthalmic surgeons at Queen's Medical Centre, Nottingham, for allowing their patients to take part in this study

The authors have no proprietary, commercial, or financial interest in the Lens Opacity Meter 701

1 Flammer J, Bebie H Lens Opacity Meter· a new instrument to quantify lens opacity *Ophthalmologica* 1987; 195: 69–72.
2 De Natale R, Flammer J, Zulauf M, Bebie T. Influence of age on the transparency of the lens in normals a population study with the help of the Lens Opacity Meter 701. *Ophthalmologica* 1988; 196: 14–8.
3 Tuft SJ, Fitzke FW, Lawrenson J, Silver J, Marshall J Quantification of lens opacification with a commercially available lensometer *Br J Ophthalmol* 1990; 74: 78–81
4 Kempthorne O *The design and analysis of experiments* New York: Wiley, 1960 54–9.

British Journal of Ophthalmology, 1990, 74, 528–531

Topical steroids in the treatment of central and paracentral corneal ulcers

T R Carmichael, Y Gelfand, N H Welsh

Department of Ophthalmology, University of the Witwatersrand, Johannesburg, Republic of South Africa
T R Carmichael
Y Gelfand
N H Welsh

Correspondence to:
Dr T R Carmichael, PO Box 2681, Alberton 1450, Republic of South Africa

Accepted for publication
11 April 1990

Abstract

During an 18-month period a prospective randomised trial was conducted on 40 selected patients with bacterial corneal ulcers. Two groups were compared: one was treated with antibiotic only and the other with antibiotic plus steroid. Complications were similar in the two groups. No delay in healing rate of the ulcers was seen with the use of topical steroid. Two methods of assessing visual improvement are discussed, but it was not possible to demonstrate a difference in visual outcome between the two groups.

The treatment of central (primarily infectious) corneal ulcers with topical steroids has remained a controversial subject since the introduction of steroids in the 1950s.[1] The use of steroids is a two-edged sword; they may protect the cornea from host inflammatory response but at the risk of enhancing the infection. There has been no controlled clinical trial to resolve the issue. This is due mainly to a lack of suitable clinical material combined with a large number of variables, such as type of ulcer, isolates, and others.

Experimental data, mainly in rabbits, suggest no adverse effects so long as an appropriate antibiotic is given concurrently with steroids. This has been shown for *Pseudomonas aeruginosa*[2,3] and *Staphylococcus aureus*[4] infections. However, Smolin *et al*[5] suggested that wound healing may be delayed and there may be prolonged replication of organisms in pseudomonas infections. Fungal infections seem adversely affected by the use of steroid because the available antifungals achieve only fungistatic levels in the cornea.[6] Clinical studies[7,8] have supported these experimental findings.

The present study compares the results of treating one group of corneal ulcer patients receiving antibiotic only with another group receiving antibiotic plus steroid.

Patients and methods

The patients included in the study had central or paracentral bacterial corneal ulcers severe enough to warrant hospital admission. Patients were excluded if they had fungal isolates, perforated ulcers or descemetocoeles, underlying viral corneal conditions, atopic ulcers, no light perception on admission, or were less than 13 years of age. On admission the patients were informed of the treatment to be given and consented to it.

Treatment consisted of Kefzol eye drops (cefazolin, fortified, 32 g/l) and gentamicin eye drops (fortified, 14 g/l) hourly, Atropine eyedrops 1% twice daily, chloromycetin eye ointment at night (2200) and twice daily multivitamin tablets (Multivites). In addition subconjunctival cefazolin (125 mg) and gentamicin (20 mg) were given on admission, the following morning, and one or two further injections as indicated by the severity of the infection. The subconjunctival antibiotics were injected separately into a bleb of lignocaine. No oral or intravenous antibiotics were used. Once accepted into the study, the patients were randomised and both groups received the same treatment for 24 hours. On the day after admission, if the steroid group was considered to be the same or improved, Maxidex eye drops (dexamethasone 0·1%) four times a day were added to their treatment and continued until healing was complete, with a minimum of two weeks. If there was frank deterioration the steroid was withheld for 24 hours and the case reassessed and so on.

ASSESSMENT OF RESULTS

Recording sheets were used to document the initial appearance of the ulcer and its size and depth by means of a drawing. The appearance and best corrected visual acuity were noted on the same sheet during the follow-up period. Follow-up was continued until the final best corrected visual acuity was determined (minimum of four weeks). All assessments were done by two doctors, which was the most objective method of assessment in view of practical limitations (rotation of doctors through teaching hospitals). In measuring visual acuity the same method with the same Snellen chart was used by both doctors.

To analyse statistically the visual acuity data visual acuity was converted to a number (see Table 1). This meant that no light perception was assigned the number 1 and 6/6 was assigned the number 15. Visions between these values were: (*a*) Snellen chart values; (*b*) counting fingers

Table 1 Visual acuities (follow-up at 2 months)

Steroid group				*Non-steroid group*			
Initial	*N.eq*	*Final*	*N.eq*	*Initial*	*N.eq*	*Final*	*N.eq*
20/80	11	20/20	15	CF 3 m	6	20/40	13
HM	3	20/200	9	HM	3	NLP	1
20/40	13	20/30	14	CF 1 m	4	CF 5 m	8
CF 4 m	7	20/200	9	20/80	11	20/40	13
LP	2	LP	2	HM	3	CF 3 m	6
HM	3	CF 1m	4	20/120	10	20/20	15
CF 4 m	7	20/40	13	HM	3	20/200	9
HM	3	CF 1 m	4	HM	3	HM	3
CF 5 m	8	20/80	11	HM	3	HM	3
20/200	9	20/120	10	20/20	15	20/20	15
LP	2	20/120	10	CF 1 m	4	20/80	11
CF 2 m	5	20/40	13	HM	3	CF 5 m	8
CF 1 m	4	20/200	9	20/20	15	20/20	15
CF 1 m	4	20/120	10				
20/200	9	20/60	12				

N.eq is numerical equivalent.

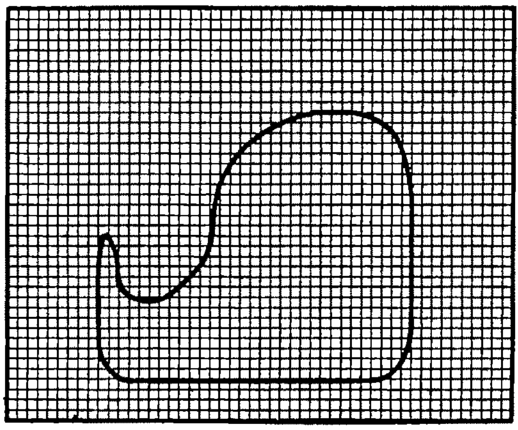


Figure 1 *Scale drawing of corneal ulcer on graph paper.*

(CF) from 1 to 5 metres; (*c*) hand movements (HM); (*d*) light perception (LP); (*e*) no light perception (NLP).

For purpose of comparison between the groups the transition, for example, between 6/24 and 6/36 is regarded as being the same as a deterioration from CF 1 m to CF 2 m.

Results of treatment were assessed in terms of: (1) complications; (2) healing rate (mm^2 of ulcer per day); (3) visual acuity.

BACTERIOLOGY

Corneal specimens were taken with a platinum spatula at the slit-lamp. These were inoculated on to blood agar and into serum broth and brain-heart infusion broth. Two glass slides were prepared, one for Gram stain and one for a special stain if required. Both base and edges of the ulcer were sampled after necrotic debris was removed. Specimens were processed by the Bacteriology Department of Baragawanath Hospital by one technician.

AREA OF ULCERS

Each ulcer was drawn to scale on to 1 mm ruled graph paper and the squares counted. This gave an area for each ulcer, on admission, based on the dimensions measured at the slit-lamp (Fig 1). The size of the ulcer in mm^2 was used in dividing the ulcers into small (under 3 mm^2), medium (3–10 mm^2) and large (over 10 mm^2) ulcers, to compare the groups further. The area of ulcer healed per day was then calculated to compare the rate of epithelialisation.

Results

There were 21 eyes in the steroid group and 19 in the non-steroid group. One patient had bilateral corneal ulcers and they were randomised separately. The groups were statistically comparable in terms of number of eyes in each group, age, and duration of inpatient treatment. There were significantly more males in the steroid group (χ^2, $p<0{\cdot}01$) (Table 2). The patients' ages ranged from 19 to 81 years. There was no significant difference between the ulcers in the two groups with respect to depth, size, positive cultures, or presence of hypopyon (Table 3). Table 4 shows that the corneal isolates obtained were similar in both groups and comparable to the isolates previously obtained in this population.[9] Complications (Table 5) were similar in the two groups.

Table 2 *Comparison of groups*

	Steroid	*Non-steroid*
No of eyes	21	19
Mean age (years)	51 6	51 4
Percentage males	90	76
Inpatient days (mean)	18	20

Table 3 *Comparison of ulcers (numbers)*

		Steroid	*Non-steroid*
Site:	Central	7	9
	Paracentral	14	10
Depth:	Outer third	10	8
	Middle third	5	9
	Inner third	6	2
Size	Small	9	8
	Medium	8	5
	Large	4	6
Hypopyon present		16	12
Positive culture		14	14

Within the steroid group one case showed descemetocoele formation the morning after admission, and, according to the protocol, steroids were not started. There was corneal perforation the following day, and, as the anterior chamber did not reform after pressure padding, a penetrating keratoplasty was performed. Corneal thinning with early descemetocoele formation made it necessary to discontinue steroids after 12 days in one case. The ulcer subsequently healed uneventfully.

One patient with a pneumococcal infection

Table 4 *Corneal cultures*

	Steroid	*Non-steroid*
Str pneumoniae	3	4
Str agalacticae		1
Str viridans	3	
Staph aureus		1
Staph epidermidis	2	3
Bacillus sp		1
Haemophilus influenzae		2
Pseudomonas paucimobilis		1
Proteus mirabilis		1
Morganella morganii		1
Serratia sp	1	
Acinetobacter anitratus	1	
Corynebacteria sp	5	1
No growth	7	5
Total	22	21

Mixed culture in steroid group *Acinetobacter anitratus* with *Staph epidermidis*
Mixed cultures in non-steroid group *Str pneumoniae* with *H influenzae Pr mirabilis* with *Staph epidermidis*

Table 5 *Complications*

	Steroid	*Non-steroid*
Perforation	1	1
Corneal thinning	1	1
Uncontrolled infection	0	2
Recurrence of infection	1	2
Persistent epithelial defect	4	3
Epithelial breakdown	1	1
Total	8	10

Persistent epithelial defect is failure of healing of the ulcer within 21 days.

Recurrence of infection is recurrence of abscess/hypopyon occurring within one week of discharge where the infective element was previously considered cleared

Epithelial breakdown is breakdown of epithelium after initial healing

One patient in the steroid group had both persistent epithelial defect and recurrent infection.

showed a persistent epithelial defect (epithelial defect over 21 days) and then presented five days after discharge with a recurrence of corneal abscess and hypopyon. This patient appears under both headings in Table 5. Persistent epithelial defects were seen in four cases. Two of these were large ulcers and healed slowly, and two had severe climatic droplet keratopathy (CDK). In one case the ulcer healed in five days, but the epithelium broke down and rehealing took a further seven days (12 days for final healing). Steroid therapy was discontinued after 12 days in the case of corneal thinning and not given in the case of corneal perforation. All other cases received full courses of topical steroid.

Within the non-steroid group a pneumococcal ulcer perforated after three days but responded to conservative treatment (pressure padding) and healed without surgery. One patient showed corneal thinning and descemetocoele formation but responded to pressure padding and healed uneventfully. Uncontrolled infection occurred in two eyes; one was a *Staph aureus* infection; in the other case the eye was eviscerated but only *Staph epidermidis* was isolated. Infection recurred in a patient whose hypopyon had cleared and who was discharged 11 days after admission with a remaining epithelial defect. This patient presented five days later with fresh corneal infiltrate and hypopyon and was readmitted. In the other patient with recurrent infection the ulcer healed within 21 days but the corneal abscess recurred and he was readmitted to hospital.

There were three cases of persistent epithelial defect, two of which were large ulcers and one showed severe CDK. The patient with epithelial breakdown also had CDK, but the ulcerated area rehealed in under 21 days.

Healing rates were calculated for 15 ulcers in the steroid group and 11 in the non-steroid group. Patients were excluded from this analysis if they showed persistent epithelial defects, as some never healed completely, and others took two or three months, which would have distorted the analysis. Patients were also excluded if they required therapy other than that in the protocol – for example, pressure padding for perforations or corneal thinning – as this might influence the rate of healing. The two patients with uncontrolled infection did not heal and were excluded from the analysis.

The only patients with complications (Table 5) that were included in the healing rate analysis were those with epithelial breakdown and one with recurrent infections in the non-steroid group. These three patients all showed healing within 21 days. This meant that six patients from the steroid group and eight from the non-steroid group were excluded. There was no significant difference when the two groups were compared by Student's *t* test. The mean healing rate for the steroid group was 0·36 mm^2/day and for the non steroid group was 0·30 mm^2/day. When the visual acuities between the two groups are compared by the numerical system in Table I, no difference could be shown. A statistically significant improvement in both groups followed treatment, as might be expected. The steroid group had an average pretreatment vision of 6 and an average post-treatment vision of 9·7 ($p < 0·001$, paired analysis by *t* test). The non-steroid group had an average 6·4 pretreatment and 9·2 post-treatment ($p < 0·01$ paired analysis by *t* test). Visual acuities were also compared by plotting scattergrams for pre- and post-treatment visual acuities for each group and fitting linear regression lines. There was again no discernible difference between the two groups, though the improvement in the steroid group was slightly greater (Fig 2). The coefficient of determination (R^2) was 53% for the steroid group and 64% for the non-steroid group.

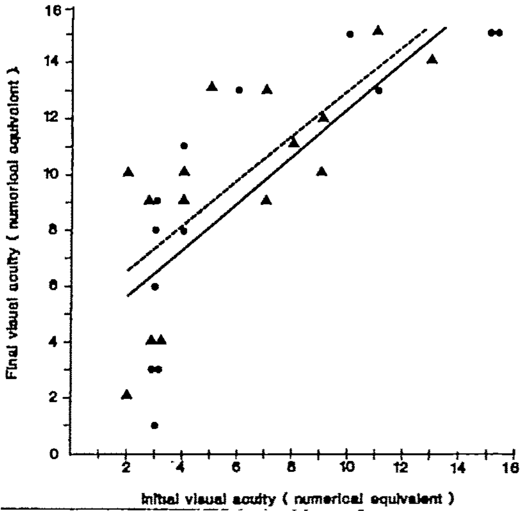


Figure 2 Scattergram with linear regression lines comparing visual improvement with and without steroids.
● *Non-steroid* ——. ▲ *Steroid* ——.

Discussion

Inflammation and subsequent scarring of the cornea may compromise vision. When designing a treatment regimen some consideration must be given to including an anti-inflammatory agent if this can be done safely. Evidence against the use of steroids include possible detrimental effect should fungal[6] or viral[10] infection be present; recurrence of pseudomonas infection[11 12]; or prolonged replication of organisms and delayed wound healing.[5] Supporting the use of steroid is the experimental evidence that pseudomonas[2 3] and *Staph aureus*[4] keratitis are not adversely affected by steroid use so long as the appropriate antibiotic is used. There are also clinical reports of the use of steroid in bacterial keratitis.[7 8] Wilson[13] mentions that topical steroids were used 'in some but not all' of the 200 bacterial corneal ulcers he treated over a 10-year period.

In the present study the two groups were similar in most respects, and the preponderance of males in the steroid group should not cause undue bias. The ulcers within each group were also comparable, though the isolates differed somewhat. Obviously the larger the groups, the greater the chance that one can collect totally comparable groups. Benefits or adverse effects of using steroids were assessed in the most objective ways possible under the circumstances. Complications within the two groups were remarkably similar, and the feared perforations and corneal thinning in the steroid treated group did not materialise.

Severe infections may recur, and this was seen with a pneumococcal ulcer in the steroid group. Recurrence of infection was otherwise associated with conditions causing persistent epithelial defects. As previously reported,[14] the severe nodular form of climatic droplet keratopathy is a common predisposing factor for corneal ulceration in this population. The plaques flake off leaving epithelial defects which are slow to heal and become reinfected. Patterson and Jones[10] reported using area of ulcers as a means of assessing the negative effects of topical steroids on dendritic keratitis. If accurate measurements are taken at the slit-lamp and the ulcers are carefully drawn to scale on to graph paper, group comparison is possible and any inaccuracies should tend to cancel out. During the present study the method was found to be consistent, and it provides another means of assessment.

No delay in healing rates was seen with the dosage of steroid used. If corneal inflammation and scarring can be reduced by the concurrent use of topical steroids, it should be possible to show an improvement in visual acuity. Two methods of comparing the visual acuities were used, but neither showed a significant difference between the groups. When visions were converted to a numerical quantity, a statistically significant improvement in vision was seen in both groups following treatment, but the steroid group did not do better. Scattergrams with linear regression lines showed very similar visual improvements in the two groups. The correlation coefficients were not particularly high, and this should be taken into account when interpreting the scattergram. In the present study reduction in neovascularisation and conjunctival inflammation and speed of resolution of corneal infiltrate and hypopyon were not measured.

CONCLUSIONS

No adverse effects were encountered with topical steroids in the dosage shown above. To demonstrate benefits from steroids a larger study would be needed and perhaps some refinements in assessment techniques. It is suggested that steroid treatment should be delayed for 24 hours to exclude rapidly deteriorating infections, allow appropriate selection of antibiotic, and exclude as many fungal infections as possible. It would seem prudent to reduce or discontinue steroid treatment if healing is delayed. Special care should be exercised when treating *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* infections, as they can become active again after an initial positive response to antibiotics. A large prospective study is needed, perhaps on a multicentric basis, to collect enough similar cases for meaningful analysis. Different steroid doses need to be assessed to optimise our approach. Complications within a steroid treated group of patients must be accepted, as the present study clearly confirms that complications will occur with and without steroid treatment.

1 Gordon DM, Mclean JM, Koteen H. Present status of corticotropin (ACTH), cortisone, and hydrocortisone in ophthalmology. *Br J Ophthalmol* 1953; 37: 85–98

2 Suie T, Taylor FW. The effect of cortisone on experimental pseudomonas corneal ulcers. *Arch Ophthalmol* 1956; 56: 53–6.

3 Davis SD, Sarff LD, Hyndiuk RA. Corticosteroid in experimentally induced pseudomonas keratitis. *Arch Ophthalmol* 1978, 96: 126–8

4 Leibowitz HM, Kupferman A. Topically administered corticosteroids effect on antibiotic-treated bacterial keratitis. *Arch Ophthalmol* 1980, 98: 1287–90

5 Smolin G, Okumoto M, Leong-Sit L. Combined gentamicin-tobramycin-corticosteroid treatment II. Effect on gentamicin-resistant pseudomonas keratitis *Arch Ophthalmol* 1980; 98: 473–4.

6 O'Day DM, Ray WA, Robinson R, Head WS. Efficacy of antifungal agents in the cornea. II. Influence of corticosteroids *Invest Ophthalmol Vis Sci* 1984, 25: 331–5.

7 Aronson SB, Moore TE Jr Corticosteroid therapy in central stromal keratitis. *Am J Ophthalmol* 1969; 67: 873–96.

8 Aronson SB, Moore TE Jr. Corticosteroids in infectious corneal disease In: Leopold IH, ed. *Symposium on ocular therapy*. St Louis. Mosby, 1972, 5: 77–89.

9 Carmichael TR, Wolpert M, Koornhof HJ. Corneal ulceration at an urban African hospital. *Br J Ophthalmol* 1985, 69: 920–6.

10 Patterson A, Jones B. The management of ocular herpes *Trans Ophthalmol Soc UK* 1967; 87: 59–83

11 Theodore FH. Points in the treatment of bacterial corneal ulcers. In: Leopold IH, ed. *Symposium on ocular therapy* St Louis: Mosby, 1972; 5: 48–54.

12 Burns RP. *Pseudomonas aeruginosa* keratitis. mixed infections of the eye *Am J Ophthalmol* 1969; 67: 257–62.

13 Wilson LA Acute bacterial infection of the eye. bacterial keratitis and endophthalmitis. *Trans Ophthalmol Soc UK* 1986; 105: 43–60.

14 Di Bisceglie AM, Carmichael TR. Factors predisposing to central corneal ulceration in a developing population *S Afr Med J* 1987; 71: 769–70.

British Journal of Ophthalmology, 1990, 74, 532–535

Antiviral drug sensitivity in ocular herpes simplex virus infection

M J Menage, E de Clercq, A van Lierde, V S Easty, J M Darville, S D Cook, D L Easty

Department of Ophthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX
M J Menage
S D Cook
D L Easty

Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium
E de Clercq
A van Lierde

Public Health Laboratory, Myrtle Road, Kingsdown, Bristol BS2 8EL
V S Easty
J M Darville

Correspondence to:
Professor D L Easty,
Bristol Eye Hospital,
Bristol BS1 2LX.

Accepted for publication 11 May 1990

Abstract

Thirty-nine herpes simplex virus (HSV) isolates were assayed for their sensitivity to 10 different antiviral agents. Of these 39 HSV isolates 10 were cultured from recipient buttons obtained at penetrating keratoplasty in patients with inactive stromal scarring due to recurrent herpetic keratitis, 25 were cultured from patients with conjunctival and ulcerative ocular infections, and the remaining four were laboratory strains with known drug sensitivity patterns, thus providing controls for the experiment. All but one of the 35 clinical isolates of HSV were type 1 and all were sensitive to the 10 antiviral agents. A single type 2 isolate from a young man with recurrent conjunctivitis proved to be resistant to a number of the antiviral agents. Since many of the clinical isolates had been exposed to multiple and protracted antiviral drug treatment, it is suggested that antiviral drug resistance in type 1 HSV ocular infection is not a significant problem.

Herpes simplex virus (HSV) resistance to antiviral drug treatment has long been suspected as a reason for therapeutic failure in herpetic keratitis. Failure to heal despite a protracted course of topical antiviral drug treatment has often been attributed to virus-drug resistance, but very few studies have looked at laboratory resistance of ocular herpetic infection. We have previously reported the isolation of HSV from 30% of corneal discs, removed during penetrating keratoplasty, of patients with scarring due to previous herpes simplex keratitis.[1-3] The demonstration of virus in apparently inactive stromal scars, despite previous long-term treatment with multiple antiviral drugs, suggests possible resistance of these isolates.

This study reports the antiviral drug sensitivity of 10 such recipient button isolates. In addition 25 isolates cultured from other conjunctival and ulcerative ocular HSV infections were included to determine the general level of antiviral drug sensitivity in our ophthalmic practice. Four laboratory strains with known drug sensitivity patterns provided controls for the experiments.

Patients and methods

Ten HSV type 1 isolates from corneal discs of patients with inactive scarring due to herpetic keratitis were collected in Bristol and Glasgow. Twenty-five HSV isolates were grown in cell culture at the Bristol Public Health Laboratory from swabs taken from patients presenting with ocular infections to the casualty department of the Bristol Eye Hospital. These were from a variety of clinical conditions (Table 1). Details of previous antiviral therapy were recorded, where possible, for both groups of isolates (Table 2). All but one of the viral isolates were shown to be type 1 by restriction endonuclease analysis using Bst I and Pvu II.[5] The only type 2 isolate was cultured from a young man with recurrent conjunctivitis and no history of genital infection.

Four laboratory strains were included as controls. The SC16[6] and KOS type 1 strains are known to be fully sensitive to all the antiviral agents. An in-vitro-derived acyclovir-resistant mutant of SC16 (kindly provided by Drs W A Blyth and T J Hill, Department of Microbiology, University of Bristol) and a multiply resistant type 2 strain, AR15, were also included. These provided both positive and negative controls for the experiment.

The 39 viral isolates were assayed for their sensitivity to ten antiviral agents (Table 3). These antiviral agents were selected on the basis of their known potential for the chemotherapy of HSV infections.[7-9]

The experimental method for assaying antiviral activity has previously been reported.[10] All assays were carried out in confluent embryonic skin-muscle fibroblast (E_6SM) cell cultures in

Table 1 Sources of viral isolates

Source	*No of cases*
Culture of recipient corneal buttons	10
Dendritic ulcer (first presentation)	11
Dendritic ulcer (recurrence)	6
Follicular conjunctivitis	7
Lid vesicles	1
Control strains	4
Total	39

Table 2 Previous treatment of patients with antiviral drugs

	Corneal discs (10)	*Casualty isolates (25)*
No previous treatment	0	17
Previous treatment	10	8
Antiviral drugs used		
ACV	5	3
IDU	5	2
TFT	4	0
Ara-A	5	0
Unknown	2	4

Table 3 Antiviral agents used in the drug sensitivity determinations[7]

1 IDU: idoxuridine, 5-iodo-2′-deoxyuridine
2 TFT: trifluridine, 5-trifluoro-2′-deoxythymidine
3 Ara-A vidarabine, 9-beta-D-arabinofuranosyladenine
4 ACV: acyclovir, 9-(2-hydroxyethoxymethyl) guanine
5 BVDU (E)-5-(2-bromivinyl)-2′-deoxyuridine
6 EDU: 5-ethyl-2′-deoxyuridine
7 DHPG 9-(1, 3-dihydroxy-2-propoxymethyl) guanine
8 CEDU. 5-(2-chloroethyl)-2′-deoxyuridine
9 PFA: foscarnet, phosphnoformate
10 (S)-HPMPA. (S)-9-(3-hydroxy-2-phosphonyl (methyoxypropyl) adenine

Table 4 Mean ID_{50} concentrations of antiviral agent for the HSV isolates

Anti-viral agents	*Recipient corneal buttons*		*Casualty infections (type 1)*		*Casualty infection (single type 2)*	*SC16 lab strain (type 1)*	*ACV resistant SC16 lab strain (type 1)*	*AR15 lab strain (type 2)*	*KOS lab strain (type1)*
	Mean	*Range*	*Mean*	*Range*					
IDU	0·20	0·07–0·37	0·29	0·07–0 70	2 00	0·09	8 94	2·83	0·30
TFT	1·55	0·53–2·00	1·54	0·37–3 74	20·00	0·37	2·83	20·00	2 00
ARA-A	12·2	3·7–20·0	9 6	1·2–22·1	11 8	3 7	11·8	11 8	14 6
ACV	0·04	0·02–0·07	0·03	0·02–0 06	0·02	0·02	20·00	0 02	0·04
BVDU	0·03	0 01–0 04	0·02	0·01–0·04	167·33	0 01	141·42	>200·00	0 02
EDU	1·59	0·53–2·00	0·77	0·20–2·00	2 00	0·26	141 42	2 00	0·70
DHPG	0·002	0·002–0 003	0·002	0·002–0 007	0 002	0·002	1·180	0 002	0·002
CEDU	0 13	0·02–0 20	0·14	0 02–0 37	4·47	0 05	>200·00	3·74	0 20
PFA	73·8	28·3–122 5	50·6	20 0–122 5	70·0	70 0	70 0	70 0	46 1
HPMPA	0·09	0·01–0·26	0·06	0 01–0 20	0 07	0 01	0 07	0 08	0 12

microtitre trays. These were inoculated with 100 $CCID_{50}$ ($CCID_{50}$=50% cell culture infective dose) of each virus for 1 h at 37°C.

Sequentially decreasing concentrations of each test compound were then added to the virus infected cell cultures. Controls for each experiment consisted of cell cultures which had been inoculated only with the test virus. The viral cytopathic effect (CPE) in each culture was recorded microscopically. In the control the infected cell cultures' viral CPE was generally completed at three to four days after viral inoculation. All experiments were repeated twice.

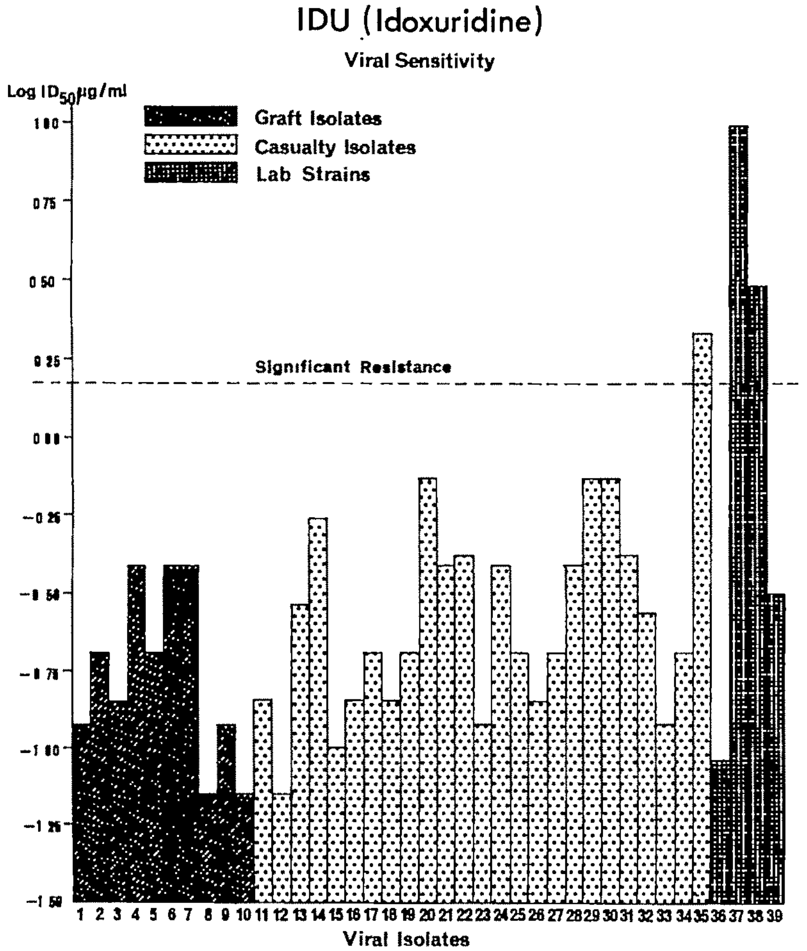


Figure 1

Figures 1–5 Sensitivity of the viral isolates to the five more commonly used antiviral drugs.

Significant resistance is defined as a five-fold increase in the ID_{50} relative to the ID_{50} of the laboratory strain KOS (viral isolate no 39). Viral isolate 35=type 2 isolate from recurrent conjunctivitis. Viral isolate 36=laboratory strain SC16. Viral isolate 37=acyclovir-resistant derivative of SC16. Viral isolate 38=type 2 laboratory strain AR15 Viral isolate 39=laboratory KOS.

Note that an arbitrary logarithmic scale is used; therefore sensitivity cannot be directly compared between separate graphs.

Antiviral drug sensitivity is expressed as the ID_{50} (50% of inhibitory dose), that is, the concentration of drug required to reduce the viral CPE by 50% at the time when complete cell destruction was noted in the control infected cell cultures.

Results

The mean ID_{50} obtained for each compound with viral isolate was calculated for the two experiments. All 10 of the viral isolates from corneal discs of inactive stromal scarring and the 24 type 1 viral isolates from ulcerative and conjunctival infections showed no significant resistance to any of the 10 antiviral agents. We found all type 1 clinical isolates were fully sensitive to the 10 antiviral agents (Table 4).

Significant resistance is defined as a five-fold increase in the ID_{50} relative to that for the KOS strain, since this control virus was known to be sensitive to all the antiviral agents used. Other workers using a similar method have defined resistance as high as a 10-fold increase in the ID_{50} relative to that for the KOS strain.[11]

The single type 2 infection from a young man with recurrent conjunctivitis showed resistance to TFT, IDU, BVDU, and CEDU (see Table 3 for abbreviations), which was similar to the resistance pattern shown by the type 2 laboratory strain AR15.

Results for the four laboratory strains were as expected with the KOS and SC16 strains showing no evidence of resistance. The acyclovir-resistant derivative of SC16 were resistant to ACV and also showed cross resistance to IDU, BVDU, EDU, CEDU, and DHPG. The type 2 AR15 strain showed resistance to TFT, IDU, BVDU, and CEDU.

The results for the five more familiar antiviral drugs are presented in Figs 1–5.

Discussion

Considerable attention has focused on the development of HSV resistance to antiviral drugs, most recently with the introduction of acyclovir to clinical practice.[12 13] Reports of acyclovir resistant clinical strains have largely been confined to immunosuppressed patients receiving high dose intravenous treatment, and sensitivity has returned on withdrawal of the acyclovir.[14 16]

Report's of laboratory proved resistance to

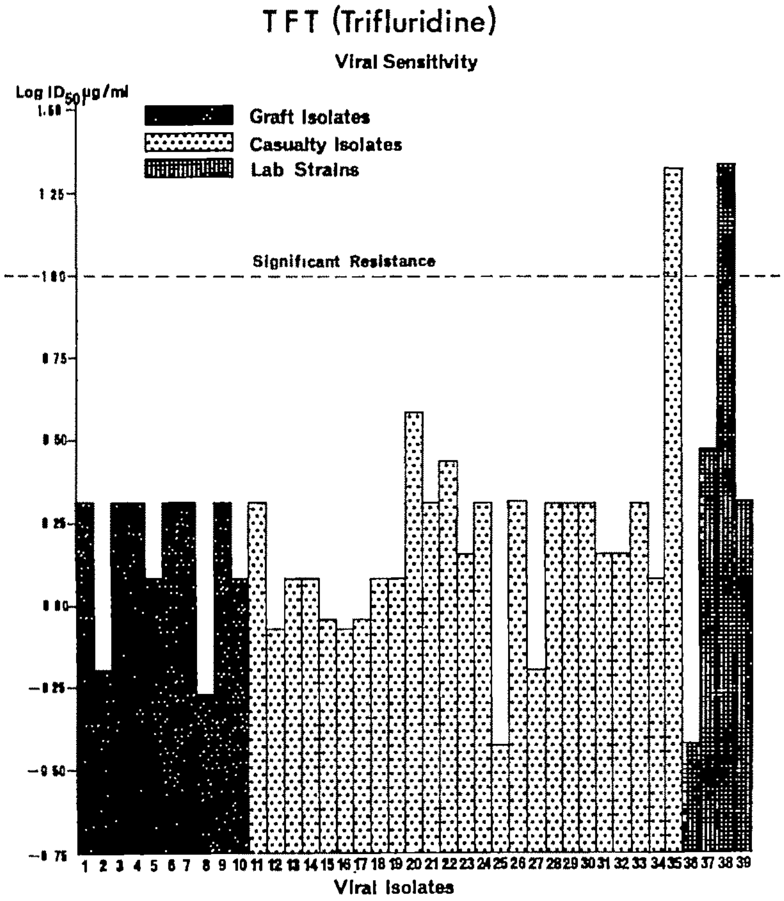


Figure 2

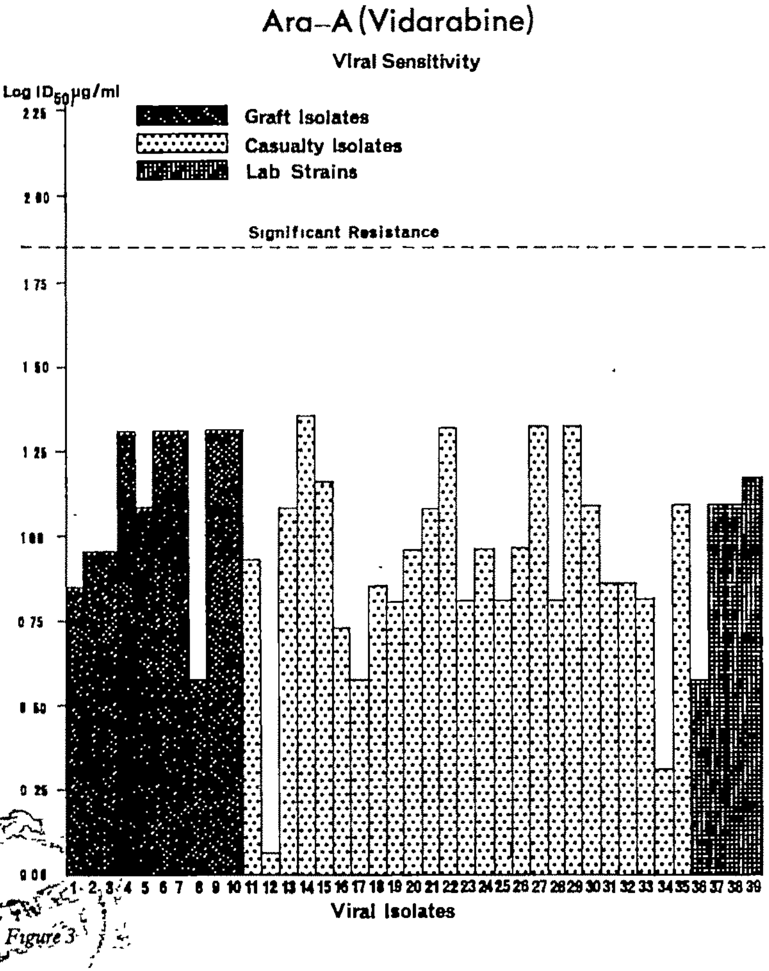


Figure 3

antivirals in ocular herpes simplex infection are very rare,[17] but failure to heal in clinical herpetic keratitis is a relatively common problem, with persistence of the infection despite apparently adequate treatment with a topical antiviral drug. A concept of 'treatment resistance' or 'clinical resistance' has been proposed in the situation where an ulcer fails to heal with apparently adequate treatment with one antiviral drug but responds well when another is used.[18 19] A complex definition of clinical resistance is necessary in order to try and exclude some of the many other causes of failure to respond to treatment.[18] These include poor stromal penetration, poor compliance, inadequate treatment, toxicity, coexisting epithelial disease, and inappropriate use of steroids. Clinical resistance rates of 37% with IDU and 11% with Ara-A have been reported.[17]

The results of our experiments indicate there is little if any evidence of resistance of type 1 ocular isolates to the commonly used antiviral agents to support the relatively common clinical experience of failure of antiviral drug treatment of herpetic keratitis. This only serves to emphasis the need for adequate delivery of sufficient antiviral agent to the virus and the other multiple causes of clinical resistance.

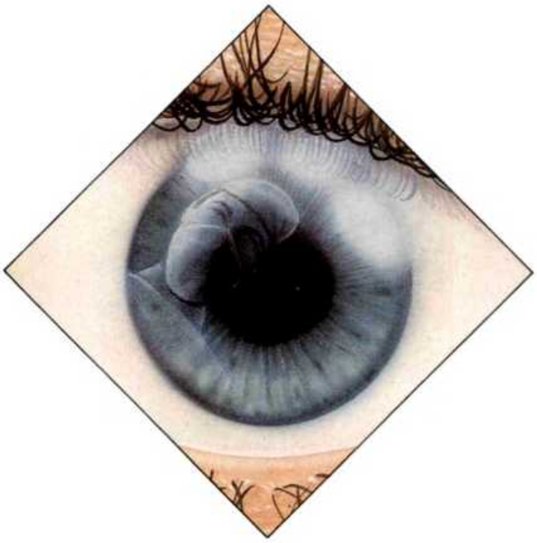
This study developed from the isolation of HSV from inactive scarring in patients with long histories of herpetic keratitis. The patients had been subjected to multiple courses of antiviral drugs over many years. The lack of resistance of the isolates indicates that repeated exposure to antiviral drugs does not easily generate virus drug resistance in ophthalmic infection.

Resistance of HSV to antiviral drugs[20] is mediated by two loci on the herpes virus genome, viral thymidine kinase and viral DNA polymerase. Thymidine kinase deficient mutants can easily be selected for in-cell culture and have occasionally been isolated from immunocompromised patients treated with acyclovir[21] but show markedly diminished pathogenicity in laboratory animals.[22] This is also the case in experimental ocular infections.[23 24] It is postulated that, if such drug-resistant HSV mutants were to emerge in the corneal stroma of patients with herpetic keratitis, their low pathogenicity would make them unlikely either to establish trigeminal ganglion infection or subsequently to reactivate from a latent stage.

The HSV isolates from conjunctival and ulcerative infections presenting to the casualty department showed no significant resistance to any of the antiviral agents. The lack of resistance to a large number of commonly used antiviral agents in all the clinical type 1 HSV infections would indicate a low incidence of virus-drug resistance in the vast majority of ocular HSV infections.

The only type 2 HSV clinical isolate in our study showed resistance to TFT, IDU, BVDU, and CEDU but was fully sensitive to the other antiviral agents, including ACV. Even the most resistant isolates tested showed sensitivity to some of the commonly used antiviral agents.

Ocular type 2 HSV infection is very rare, and no other similar isolates had been obtained at the time of the experiment. Some studies have



. . . WHEN YOU CHOOSE THE RIGHT SOLUTION

Alcon

BSS®

BALANCED SALT SOLUTION

With most ocular irrigation solutions corneal clouding can begin within a few minutes of commencing surgery. Whilst this clouding is usually reversible, it does make intraocular surgery such as cataract surgery more difficult because the detail within the eye is greatly obscured.[1]

BSS overcomes this problem. It has been designed to be similar to the physiological fluids that naturally bathe the eye. BSS therefore maintains a clear cornea and ensures that you can see the fine detail within the eye throughout surgery.[1,2]

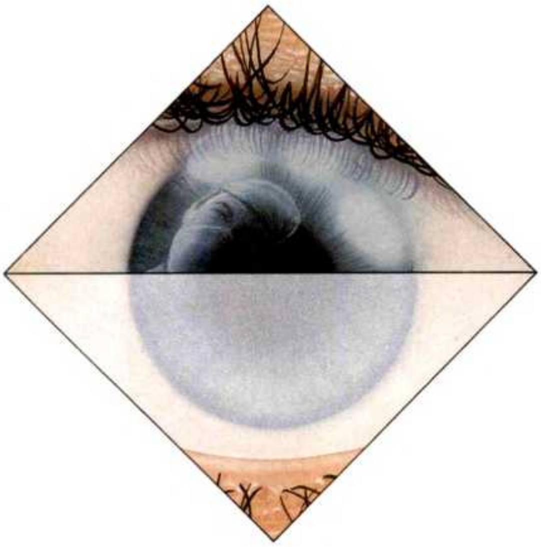
250ML AND 500ML BOTTLES

BSS is now available in a new 250ml size, specifically designed for the longer cataract procedures. One bottle will last through the whole operation and results in less wastage. BSS is now available in a full range of sizes ideal for all your surgical requirements.

So don't let the wrong solution cloud your vision.

Remember – only Alcon Balanced Salt Solution is – BSS.

® Registered Trademark.



THE DIFFERENCE IS CLEAR...

Prescribing Information.

Presentation: A sterile physiological balanced salt solution which is isotonic to the tissues of the eye. Containing Sodium Chloride Ph.Eur. 0.64%, Potassium Chloride Ph.Eur. 0.075%, Calcium Chloride Ph.Eur. 0.048%, Magnesium Chloride Hexahydrate Ph.Eur. 0.03%, Sodium Acetate Ph.Eur. 0.39%, Sodium Citrate Ph.Eur. 0.17% and Water for Injection Ph.Eur.

Uses: As a physiologic irrigating solution.

Dosage and Administration: Sufficient to produce the required irrigation.

Contra-indications, Warnings, etc:

There are no specific contra-indications for this product. When the corneal endothelium is abnormal, irrigation or any trauma may result in bullous keratopathy.

Not for intravenous infusion.

Contains no preservatives and should not be re-used.

Legal Category: P

Package Quantities: 15ml and 30ml Steri-Unit Drop-Tainer dispensers and 250ml and 500ml glass infusion bottles.

Product Licence Number: 15ml and 30ml Steri-Unit Drop-Tainer 0649/0007; 250ml and 500ml glass infusion bottles 0649/0099.

References

1. McDonnell PJ, Spalton DJ. Corneal clarity during extracapsular cataract surgery. Implant & Refractive Surgery, 1987; **6** (1): 9-13.
2. McDermott ML, et al. Ophthalmic Irrigants: A current review and update. Ophthalmic Surgery, 1988; **19** (10): 724-733.

Company Name and Address:

Alcon Laboratories (UK) Ltd,
Imperial Way, Watford,
Herts WD2 4YR.

Alcon

BSS®

BALANCED SALT SOLUTION

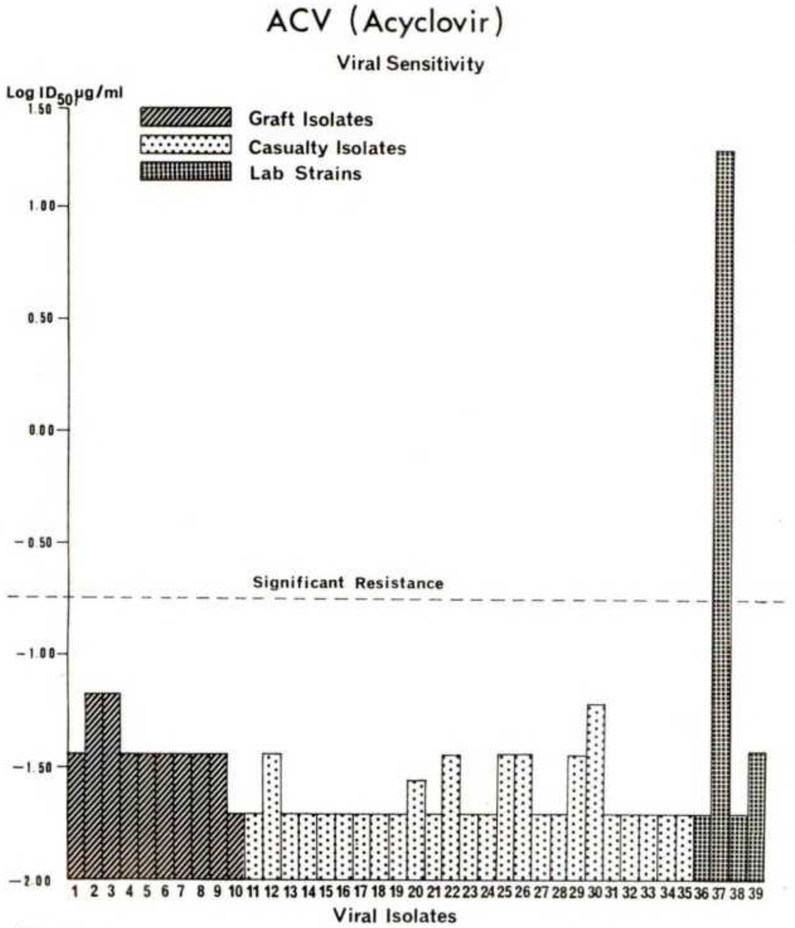


Figure 4

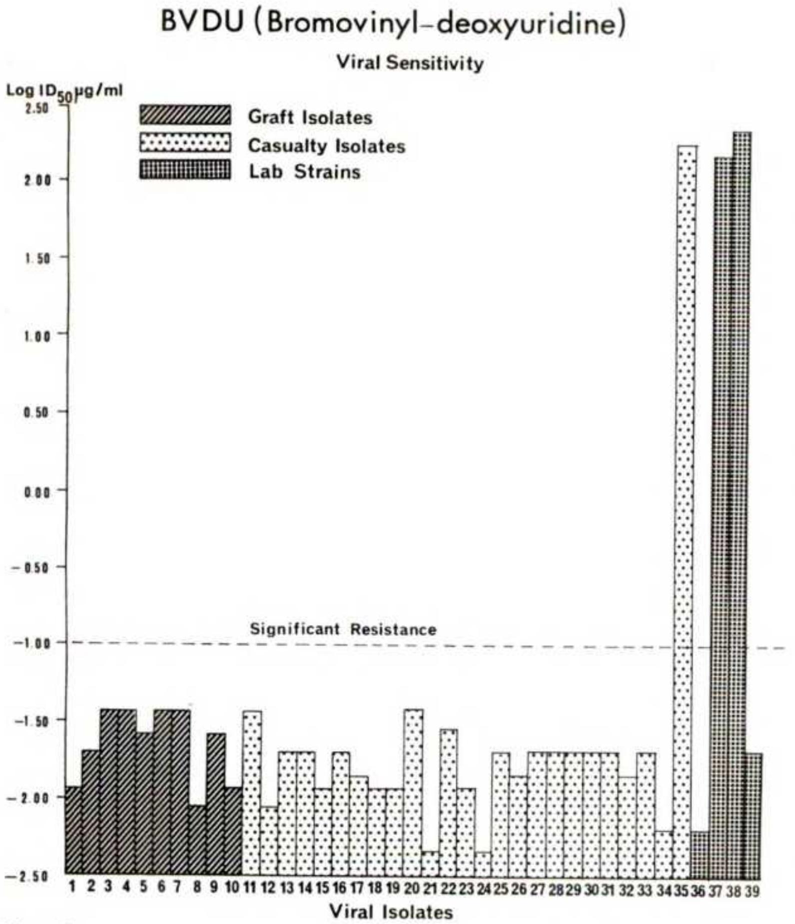


Figure 5

shown that type 2 HSV isolates have higher ID_{50} values than type 1 isolates when tested for acyclovir sensitivity,[14] and there is some evidence that breakthrough infections in patients on prophylactic acyclovir for genital type 2 HSV infections show increased resistance[16], but there is scant information on ocular infections.

It is unwise to draw any conclusions from a single result, but this obviously offers scope for further investigation into both the frequency of ocular type 2 herpetic infection and the level of resistance to antiviral drugs.

In conclusion, our results suggest that virus-drug resistance is not a significant problem in ocular type 1 HSV infections.

1 Shimeld C, Tullo AB, Easty DL, Thomsitt J. Isolation of herpes simplex virus from the cornea in chronic stromal keratitis. *Br J Ophthalmol* 1982; **66:** 643–7.
2 Tullo AB, Easty DL, Shimeld C, Stirling PE, Darville JM. Isolation of herpes simplex virus from corneal discs of patients with chronic stromal keratitis. *Trans Ophthalmol Soc UK* 1985; **104:** 159–65.
3 Easty DL, Shimeld C, Claoue CMP, Menage MJ. Herpes simplex virus isolation in chronic stromal keratitis: human and laboratory studies. *Curr Eye Res* 1987; **6:** 69–74.
4 Cook SD. PhD Thesis. University of Glasgow: 1988.
5 Darville JM A miniaturised and simplified technique for typing and subtyping herpes simplex virus. *J Clin Pathol* 1983; **36:** 929–34.
6 Hill TJ, Field HJ, Blyth WA. Acute and recurrent infection with herpes simplex virus in the mouse: a model for studying latency and recurrent disease. *J Gen Virol* 1975; **28:** 341–53.
7 De Clercq E. Antiviral nucleoside analogs. *ISI Atlas of Science: Pharmacology* 1987; **1:** 20–4.
8 De Clercq E. Recent advances in the search for selective antiviral agents. In: Testa B, ed. *Advances in drug research.* London: Academic Press, 1988; **17:** 1–59.
9 De Clercq E. Antiviral agents: facts and prospects. In: Reeves DS, Geddes AM, eds. *Recent advances in infection.* Edinburgh: Churchill Livingstone, 1989: 45–61.
10 De Clercq E, Descamps J, Verhelst G, Walker RT, Jones AS, Torrence PF, Shugar D. Comparative efficacy of antiherpes drugs against different strains of herpes simplex virus. *J Infect Dis* 1980; **141:** 563–74.
11 Field HJ. A perspective on resistance to acyclovir in herpes simplex virus. *J Antimicrob Chem* 1983; 12 (suppl B): 129–35.
12 Timbury MC. Acyclovir. *Br Med J* 1982; **285:** 1223–4.
13 Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED. Herpes simplex keratitis. *Ophthalmology* 1983; **90:** 700–6.
14 Crumpacker C. Resistance of herpes simplex virus to anti-viral agents. *Drugs* 1983; **26:** 373–7.
15 Dekker C, Nixon Ellis M, McLaren C, Hunter G, Rogers J, Barry DW. Virus resistance in clinical practice. *J Antimicrob Chem* 1983; **12:** 137–52.
16 Dorsky DI, Crumpacker CS. Drugs five years later: acyclovir. *Ann Intern Med* 1987; **107:** 859–74.
17 McGill JI, Ogilvie M. Viral drug resistance in herpes simplex ulceration. In: Trevor-Roper P, ed. *VIth Congress of the European Society for Ophthalmology.* London: Royal Society of Medicine, 1980: 781–4.
18 McGill JI, Coster D, Frauenfelder T, Holt-Wilson AD, Williams H, Jones BR. Adenine arabinoside in the management of herpetic keratitis. *Trans Ophthalmol Soc UK* 1975; **95:** 246–9.
19 McGill JI, Tormey P. Use of acyclovir in herpetic ocular infection. *Am J Med* 1982; **20:** 286–9.
20 De Clercq E. Virus drug resistance: thymidine kinase deficient (TK−) mutants of herpes simplex virus. Therapeutic approaches. *Ann Ist Super Sanita* 1987; **23:** 841–8.
21 Vinckier F, Boogaerts M, De Clerck D, De Clercq E. Chronic herpetic infection in an immunocompromised patient: report of a case. *J Oral Maxillofac Surg* 1987; **45:** 723–8.
22 Field HJ, Darby G. Pathogenicity in mice of strains of herpes simplex virus which are resistant to acyclovir in vitro and in vivo. *Antimicrob Agents Chemother* 1980; **17:** 209–16.
23 Gordon YJ, Armstrong JA, Brown SI, Becker Y. The role of herpes virus type I thymidine kinase in experimental ocular infections. *Am J Ophthalmol* 1983; **95:** 175–81.
24 Maudgal PC, De Clercq E, Huyghe P. Efficacy of (S)-HPMPA against thymidine kinase-deficient herpes simplex virus keratitis. *Invest Ophthalmol Vis Sci* 1987; **28:** 243–8.

CENTRAL LIBRARY

British Journal of Ophthalmology, 1990, **74**, 536–537

Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis

Richard F Spaide, John E Skerry, Lawrence A Yannuzzi, Janet T DeRosa

Abstract

The prevalence of the HLA-B7 and HLA-DR2 specificities in 17 unrelated patients with multifocal choroiditis and panuveitis, 11 with and six without subretinal neovascularisation, was evaluated and compared with those of two different groups. The first group was 17 patients with subretinal neovascularisation associated with presumed ocular histoplasmosis syndrome, and the second was a group of 105 eye patients with no retinal disease. HLA-DR2 was not found in any patient with multifocal choroiditis and panuveitis, but it was found in 13 patients with presumed ocular histoplasmosis syndrome ($p=6{\cdot}72\times10^{-5}$, comparison of the groups with subretinal neovascularisation). The lack of HLA-DR2 was also significant in comparison with the control group of eye patients ($p=0{\cdot}041$). This study suggests that patients with multifocal choroiditis and panuveitis and presumed ocular histoplasmosis syndrome have differing genetic predispositions, though the fundus pictures in these entities have many similarities.

Multifocal choroiditis and panuveitis,[1] like presumed ocular histoplasmosis syndrome, causes multiple focal sharply circumscribed areas of choroidal atrophy and is associated with subretinal neovascularisation. Unlike presumed ocular histoplasmosis syndrome (POHS), patients with multifocal choroiditis and panuveitis (MCP) have inflammation of the anterior chamber and vitreous. In addition patients with MCP are more likely to be young myopic women, to have recurrent crops of new atrophic chorioretinal lesions,[2] and most to have negative reactions to *Histoplasma capsulatum* tests.[1]

Peripheral atrophic scarring in POHS has been associated with an increased prevalence of the HLA-DR2 antigen.[3] Subretinal neovascularisation in POHS has been associated with an increased prevalence of the HLA-B7 and HLA-DR2 antigens.[3,4] We tested 17 patients with multifocal choroiditis and panuveitis to determine possible HLA-B7 and HLA-DR2 associations.

Patients and methods

The patients were examined at the Manhattan Eye, Ear, and Throat Hospital or referred to the private practice of one of the investigators from 1983 until the present time as a part of a larger study of subretinal neovascularisation. Presumed ocular histoplasmosis syndrome was diagnosed in patients when there were atrophic chorioretinal spots, no intraocular inflammation, and when the histoplasmin skin test was positive (histoplasmin antigen, Parke-Davis, standardised to US Reference Standard, Lot H-42 (1:100), US Public Health Service, National Center for Disease Control). Multifocal choroiditis and panuveitis was diagnosed if the patient had atrophic chorioretinal spots and recurrent bouts of anterior chamber or vitreal inflammation. Histoplasmosis complement fixation titres were tested on seven patients (New York State Department of Health Mycologic Serology Laboratory), and eight of the MCP patients had histoplasmin skin tests. All histoplasmosis tests were negative in the patients with MCP. The group of control eye patients were obtained from the Manhattan Eye, Ear, and Throat Hospital and from the private practice of one of the investigators, and none of these patients had a history of uveitis or retinal disease.

Blood was drawn from the patients, and the standard National Institutes of Health (NIH) lymphocytotoxicity assay was employed for HLA typing for B7 and DR2 (performed by

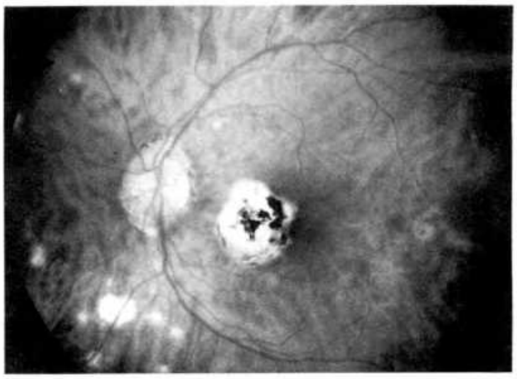


Figure 1A

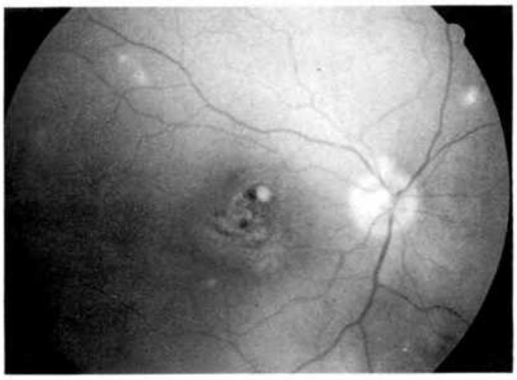


Figure 1B

Figure 1: Comparative photographs showing two patients with atrophic chorioretinal spots and disciform scarring. A: Presumed ocular histoplasmosis syndrome. B: Multifocal choroiditis and panuveitis. Patient A had a positive histoplasmin skin test. Patient B had a negative histoplasmin skin test and a recurrent intraocular inflammation.

LuEsther Mertz Retina Research Fund and Macula Foundation of the Manhattan Eye, Ear, and Throat Hospital, New York
R F Spaide
J E Skerry
L A Yannuzzi
J T DeRosa

Correspondence to:
Richard F Spaide, MD, Retina Department, Manhattan Eye, Ear, and Throat Hospital, 210 East 64th Street, New York, NY 10021, USA.

Accepted for publication 11 April 1990

Rogosin Institute, Laboratory of Immunogenetics and Transplantation, New York, New York). Cases and controls signed an informed consent for participation in this study. The consent and study design were approved by the Institutional Review Board of Manhattan Eye, Ear, and Throat Hospital.

Categorical data were analysed by the 2-tailed Fisher's exact test,[5] and a p value of 0·05 or less was considered significant.

Results

The average age of the 17 MCP patients was 34·2 years (SD 15·5 years); 15 were females, 10 were myopic. Two patients had unilateral disease, and one of these had myopia only in the affected eye. All patients had a history of vitritis, and nine had a history of anterior uveitis.

No patient with MCP had HLA-DR2, while 13 of the 17 patients (76%) with POHS and subretinal neovascularisation had HLA-DR2. In an attempt to compare similar patients we compared the 11 patients with MCP and subretinal neovascularisation with the 17 patients with POHS and subretinal neovascularisation. The prevalence of HLA-DR2 was significantly greater in the POHS group ($p=6·72\times10^{-5}$).

HLA-DR2 was found in 20% of the 105 eye patients used as a control, a frequency that is signficantly greater than in patients with MCP (p=0·041). HLA-B7 was found in two patients with MCP (11·8%), which was less than in patients with presumed ocular histoplasmosis (8 of 17, 47%) but this difference did not reach statistical significance (p=0·057). Sixteen of the group of 105 eye patients used as a control had HLA-B7 (15·2%), which was not significantly different from that in patients with MCP (p=0·995).

Discussion

In our patient group and in other studies[3,4] HLA-B7 shows a weaker association with POHS than does HLA-DR2. The prevalence of HLA-B7 in patients with multifocal choroiditis and panuveitis was less than the POHS group, but the p value did not reach statistical significance (p=0·057). The numbers of MCP and POHS patients are admittedly small, because multifocal choroiditis and panuveitis is an uncommon disease, and the New York area is not endemic for histoplasmosis. Previous studies have linked HLA-B7 with POHS, but they did not evaluate the effects of the strong linkage disequilibrium between HLA-B7 and HLA-DR2[6] and the confounding introduced by this linkage disequilibrium. HLA-DR2 shows a strong association with POHS, and it is possible that HLA-B7 seems to show a correlation with POHS because of the linkage disequilibrium between HLA-DR2 and HLA-B7.

In our group of patients and in another study HLA-DR2 showed a strong association with subretinal neovascularisation in POHS, suggesting that the presence of HLA-DR2 is a risk factor for the development of POHS. Conversely, no patient with multifocal choroiditis and panuveitis had HLA-DR2. (Although the best point estimate for the true prevalence of HLA-DR2 in the patients is zero, the 95% confidence interval extends from 0 to 0·185).[7] The striking differences in the expression of HLA-DR2 between these two groups suggests that the patients have different genetic predispositions even though the predominant ocular findings in both are atrophic spots and subretinal neovascularisation. This finding may be useful clinically in helping make the diagnosis of MCP. There was a less striking but statistically significant decrease in the prevalence of HLA-DR2 in MCP as compared with the 105 control patients. No aetiological agent has been isolated in MCP, but in one study all 10 patients with MCP had positive IgM or Epstein-Barr early antigen antibody titres while showing signs of being previously exposed to the virus (elevated IgG viral capsid antigen antibody titres).[8] Multifocal choroiditis and panuveitis might be caused by the Epstein-Barr virus or a yet unidentified factor in people with certain risk factors, that is, those with female sex, myopia, and a decreased prevalence of HLA-DR2.

1 Dreyer FR, Gass DM. Multifocal choroiditis and panuveitis. A syndrome that mimics ocular histoplasmosis *Arch Ophthalmol* 1984; **102**: 1776–84

2 Morgan CM, Schatz H. Recurrent multifocal choroiditis. *Ophthalmology* 1985, **93**: 1138–43.

3 Meredith TA, Smith RE, Duquesnoy RJ Association of HLA-DRw2 antigen with presumed ocular histoplasmosis *Am J Ophthalmol* 1980; **89**: 70–6

4 Meredith TA, Duquesnoy RJ HLA associations with presumed ocular histoplasmosis. In Fine SL, Ownes SL, eds *Management of retinal vascular and macular disorders* Baltimore Williams and Wilkins, 1983, 159–60

5 Fleiss JL. *Statistical methods for rates and proportions.* 2nd ed New York: Wiley, 1981 112–37

6 Baur MP, Neugebauer M, Albert ED. Reference tables of two-locus haplotype frequencies for all MHC marker foci In Bauer MP, Albert ED, Mayr WR, eds. *Histocompatibility testing 1984*. Berlin Springer, 1984: 677–743

7 Staehling N, Sullivan KM *Exact binomial confidence interval for proportions, version 1 0.* Atlanta Centers for Disease Control, 1988.

8 Tiedeman JS. Epstein-Barr viral antibodies in multifocal choroiditis and panuveitis. *Am J Ophthalmol* 1987; **103**: 659–63

British Journal of Ophthalmology, 1990, 74, 538–541

Radioimmunoscintigraphy and immunohistochemistry with melanoma-associated monoclonal antibodies in choroidal melanoma: a comparison of the clinical and immunohistochemical results

D F Schaling, J P van der Pol, M J Jager, M J P G van Kroonenburgh, J A Oosterhuis, D J Ruiter

Department of Ophthalmology, University Hospital, Leiden, The Netherlands
D F Schaling
J A Oosterhuis

Department of Ophthalmology, Academic Medical Centre, Amsterdam, The Netherlands
J P van der Pol
M J Jager

Department of Microbiology and Immunology, University of Miami, Florida, USA
M J Jager

Department of Diagnostic Radiology, Divison of Nuclear Medicine, University Hospital, Leiden, The Netherlands
M J P G van Kroonenburgh

Institute of Pathology, University of Nijmegen, The Netherlands
D J Ruiter

Correspondence to:
D F Schaling, MD, FC
Donders Institute of Ophthalmology, University Hospital Utrecht,
Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.

Accepted for publication
10 April 1990

Abstract

Radioimmunoscintigraphy with monoclonal antibodies (MoAbs) to melanoma associated antigens is a new technique that can be used as an additional test to detect ocular melanomas in clinically difficult cases. Immunoscintigraphy with ^{99m}technetium-labelled monoclonal antibody fragments of MoAb 225·28S in 14 patients with melanoma yielded a positive image in only six cases (43%). The expression of high molecular weight melanoma-associated antigen (HMW-MAA) was immunohistochemically assessed in melanoma tissue obtained from these 14 patients to find a possible correlation between the results of immunoscintigraphy and expression of the HMW-MAA. The melanoma tissues were immunohistochemically stained by a sensitive immunoperoxidase procedure with three different monoclonal antibodies to the HMW-MAA: 225·28S, Mel-14, and AMF-6. Expression of the antigen detected by MoAb 225·28S was found in 13 of 14 melanomas; the MoAbMel-14 reacted positively with all 14 melanomas; staining with MoAb AMF-6 was achieved in 10 melanomas. No correlation was found between the immunohistochemical staining results, the conventional histopathological findings, and the immunoscintigraphic results. The immunohistochemical staining results suggest that anti-HMW-MAA MoAbs bind to the melanoma tissue and are therefore potentially suitable for immunoscintigraphy.

Since the development of the hybridoma technology[1] several monoclonal antibodies (MoAbs) have been raised against cutaneous melanoma.[2-9] Only a few MoAbs have been developed against uveal melanoma.[10] A major reason for the limited number of antibodies to uveal melanoma is the problem of establishing a uveal melanoma cell line which facilitates the induction and characterisation of uveal melanoma specific MoAbs. Fortunately several MoAbs of cutaneous melanoma show cross reactivity with uveal melanoma tissue.[11-13]

Antibodies such as 225·28S are directed to a high molecular weight melanoma-associated antigen (HMW-MAA),[3] which is expressed in about 90% of the cutaneous melanomas.[14,15] Expression of the HMW-MAA in uveal melanoma was found to occur in 40 to 50% of cases.[12,16]

The ^{99m}technetium-labelled antibody 225·28S has been used for immunoscintigraphy in uveal melanoma patients and yielded detection percentages from 37% to 64%.[17-19] The use of sophisticated equipment like single photon emission computerised tomography (SPECT) or a 'double pinhole' collimator enhanced the detection percentages to 73% to 92%.[17-19] In view of the results of the relatively low in-situ expression of the HMW-MAA in uveal melanoma in previous studies[12,16] the detection rates of immunoscintigraphy with MoAb 225·28S in patients seem to be surprisingly high. Since we could obtain tumour tissue from 14 patients who participated in a previous immunoscintigraphic study with MoAb 225·28S[19] we determined the expression of the HMW-MAA immunohistochemically in these tissues. In addition to monoclonal antibody 225·28S to the HMW-MAA, MoAb Mel-14[2] and MoAb AMF-6[20] were used for immunohistochemical analysis.

Patients and methods

IMMUNOSCINTIGRAPHY

Radioimmunoscintigraphy was performed in 14 melanoma patients with MoAb 225·28S from an instant labelling kit (Technemab-K-1; Sorin Biomedica, Italy). For immunoscintigraphy 250–350 µg of antibody labelled with 740 MBq ^{99m}-technetium was administered by means of a slow intraveous injection. For more detailed information on the immunoscintigraphy we refer to a previous publication.[19]

HISTOPATHOLOGY

Specimens of uveal melanomas from the same 14 patients were obtained after enucleation of the eye. The enucleations were performed at the Leiden University Hospital or at the Academic Medical Centre of Amsterdam. A portion of each specimen was snap-frozen and stored at −20°C for immunohistochemical analysis. The remainder of each tumour was processed for conventional histopathological examination.

The histopathological diagnosis was assessed on paraffin and/or celloidin sections. Cell type was recorded as spindle cell, epithelioid cell, or mixed cell type. Pigmentation was scored as absent, less than half of the cells pigmented, more than half of the cells pigmented, or heavily pigmented. In addition invasion was scored as absent, slight (less than 25% of the scleral thickness), moderate (approximately 50%), deep (approximately 75%), or episcleral.

IMMUNOPEROXIDASE STUDY

Frozen sections 4 μm thick were air dried and fixed in acetone for 10 min.[20] Sections were incubated for 60 min at room temperature with MoAb diluted in phosphate buffered saline and then for 30 min with rabbit-mouse immunoglobulin-horse-radish peroxidase conjugate (Tago, Sanbio BV, Uden, The Netherlands). Between the two incubations the sections were washed three times with phosphate buffered saline (pH 7·4). Staining was achieved by incubation of sections for 10 min in an acetate buffer solution (pH 5·0) that contained 3-amino-9-ethyl-carbazole (AEC). Alternatively staining was performed by incubation of sections in a phosphate imidazole buffer solution (pH 7·6) that contained diamino-benzidine (DAB). Finally, the sections were washed, counterstained in Mayer's haematoxylin, and mounted in Aquamount (Gurr, BDH Chemicals Ltd, Poole, England). As a negative control a section was incubated with irrelevant MoAbs instead of anti-HMW-MAA MoAbs as the first step. Sections of cutaneous melanoma were used as positive controls.

The results of both the AEC and DAB staining methods were compared. The percentage of stained tumour cells was estimated independently by two observers. Differences in results between the observers were less than 10%. In addition the intensity of cellular staining was assessed. Correlations between expression of different antigens were assessed by the Kendall rank correlation procedure. The results of the two staining methods were analysed by Wilcoxon's paired signed ranks test.

MONOCLONAL ANTIBODIES

The MoAb 225·28S was tested in the form provided as a ready-to-use kit for clinical use by Sorin Biomedica, and in the pure form as provided by Dr S Ferrone. Prior to immunohistochemistry with MoAb 225·28S from the ready-to-use kit ion exchange chromatography by means of a DEAE-Sephadex A25 column was performed. This procedure is routinely performed after labelling the antibody with tc^{99m}-pertechnetate for immunoscintigraphy to reduce the amount of free pertechnetate. Ion exchange chromatography was performed to check its influence on the antibody's immunoreactivity. The two batches of antibody 225·28S were compared by Wilcoxon's paired signed ranks test. Two other antibodies, Mel-14 and AMF-6 to high molecular weight melanoma-associated antigen were obtained from Dr S Carrel and Dr C Figdor.

Results

The results of immunohistochemistry, immunoscintigraphy (planar scintigraphy), and histology are summarised in Table I. With planar scintigraphy six of 14 melanomas could be visualised. On immunohistochemistry (diamino-benzidine staining with 225·28S antibody from the ready-to-use kit) 13 of 14 melanomas (92%) showed expression of the antigen to which MoAb 225·28S is directed. Immunohistochemistry with the pure antibody 225·28S showed expression of the HMW-MAA in 12 of 14 melanomas. The numbers of positively staining cells with the two batches of antibody 225·28S did not differ significantly (Wilcoxon's paired signed ranks test, $p=0·00033$). Expression of the antigens detected by the MoAb Mel-14 and AMF-6 was found in 14 and 10 melanomas, respectively.

The Kendall rank correlation procedure was used to assess a possible correlation between 'detection on planar scintigraphy' and the following parameters: tumour prominence, pigmentation, cell type, expression of MoAb 225·28S in cells, expression of MoAb 225·28S in vessels, expression of Mel-14 cells, and expression of AMF-6 cells. No correlation between any of these parameters and detection on scintigraphy was found. The expression of MoAb 225·28S was positively correlated with the expression of Mel-14 (14 observations, Kendall rank correlation procedure, $p=0·037$). The expression of AMF-6 was not correlated to the expression of either Mel-14 or 225·28S (14 observations).

Table 1 Immunohistochemistry, scintigraphy and histology

Patient	*Sex/ age*	*DAB staining (Ferrone) 225·28S*		*DAB staining (Sorin) 225 28S*			*AEC staining 225 28S (Ferrone)*		*DAB staining Mel·14*		*DAB staining AMF·6*		*Scintigraphy graphy*	*Tumour prominence (mm)*	*Cell type*	*Pigmentation*	*Scleral invasion*
		*	†	*	†	‡	*	†	*	†	*	†					
1	F/58	80	1	30	1	1	50	1	100	2	100	2	Neg	5·5	Spindle	1	Moderate
2	M/75	100	1	100	1	–	10	1	100	2	30	1	Neg	2·2	Spindle	2	Slight
3	F/65	90	1	10	1	2	80	2	20	2	0	–	Pos	15	Mixed	1	§
4	M/42	80	1	50	1	0	40	1	25	1	0	–	Pos	3	Mixed	0	Deep
5	M/65	90	2	80	3	2	50	1	100	2	10	1	Pos	7·9	Epithel	2	Episcleral
6	M/76	0	–	5	1	2	5	1	20	1	0	–	Neg	10	Epithel	1	Slight
7	F/56	100	1	100	2	2	5	1	100	2	10	1	Neg	9·5	Mixed	1	Absent
8	M/76	90	1	100	2	2	40	1	100	2	20	1	Pos	15	Mixed	1	Slight
9	M/68	60	1	40	1	3	50	1	100	1	20	1	Neg	11	Mixed	2	Episcleral
10	M/65	70	1	75	1	–	0	–	90	2	70	1	Neg	8	Spindle	3	Deep
11	M/75	70	1	80	1	2	30	1	100	1	10	1	Neg	3·5	Mixed	3	Episcleral
12	F/64	80	1	80	2	2	40	1	100	1	10	1	Pos	7·5	Mixed	2	Episcleral
13	F/65	100	2	100	2	2	70	1	100	2	80	1	Neg	4·9	Mixed	2	Slight
14	F/69	0	–	0	–	1	0	–	100	1	0	–	Pos	6	Mixed	1	Moderate

*Percentage of positively staining cells. †Intensity of staining (1=weak, 2=moderate, 3=strong). ‡Intensity of vessel staining (1=weak, 2=moderate, 3=strong, –=not assessable, owing to heavy pigmentation or cell staining §Could not be determined owing to preparational artefact.

Staining of the tumour vasculature with MoAb 225·28S was found in 11 out of 14 cases. In two cases staining of the vessels could not be determined owing to heavy pigmentation of the tumour or diffuse cellular staining with the MoAb.

Discussion

The expression of the antigen detected by MoAb 225·28S in 13 out of 14 melanomas (92%) in the immunohistochemical study is in agreement with the results of one study (83% expression),[13] but two other studies showed a much lower expression of the antigen in uveal melanomas (50% and 41% expression respectively).[12,16] The percentage of positively staining cells per tumour is also higher in the present study than in a previous study.[12] A major reason for the difference between the results of this study and of the previous study[12] may be the use of diaminobenzidine staining in the present study, which proved to be much more sensitive than 3-amino-9-ethyl-carbazole. The results of this study indicate that the antibody 225·28S may be useful in immunoscintigraphic diagnosis of uveal melanoma, whereas previous studies showed only a limited expression of the HMW-MAA in uveal melanoma.[12-16]

The expression of the HMW-MAA in choroidal and cutaneous melanoma vessels has been previously shown with use of the 225–28S antibody.[12,21] An immunoelectron microscopic study revealed that the HMW-MAA is located in the mural pericytes surrounding the endothelial cells.[21]

The expression of antigen detected by Mel-14 in this study is in agreement with a previous study.[2] The expression of Mel-14 was correlated with the expression of the antigen detected by 225·28S (Kendall rank correlation procedure, p=0·037). The high antigen expression makes the Mel-14 antibody suitable for immunodiagnosis.

Expression of the antigen detected by AMF-6, which is at present called NKI-M6, was higher than the expression previously found.[22]

No correlation was found between tumour detection on scintigraphy with MoAb 225·28S and antigen expression for MoAb 225·28S. Such a correlation was previously found in cutaneous melanoma.[23] Since we observed expression of the HMW-MAA in this study in 92% of the cases, the detection of six of 14 melanomas by planar scintigraphy with labelled MoAb 225·28S is low. In one melanoma which could be imaged by planar scintigraphy and SPECT no expression of HMW-MAA was seen immunohistochemically (Table I). Heterogenous expression of HMW-MAA in the tumour may explain this difference.[12] On the other hand the expression of HMW-MAA in the tumour vessels may have been responsible for the positive image. Local factors such as vascular perfusion, necrosis, or the presence of an inflammatory infiltrate may influence adequate uptake of antibody in vivo. Necrosis or inflammatory infiltrate was scarcely present in our material.

Scintigraphy results of another study showed a higher detection rate with MoAb 225·28S. An explanation for this difference may be the performance of three scans after injection of the antibody[24] as compared with one scan in our study.[19] Performance of several scans at standard consecutive time intervals may provide information on the distribution of activity in the course of time. A specific activity in the vessels is high directly after injection of the antibody and then decreases, while a specific binding of antibody to the antigen needs some time to become established, and specific tracer uptake will increase on the consecutive images.

An important limiting factor is the high nonspecific background activity in the nasopharyngeal region, but the use of single photon emission computerised tomography enables the physician adequately to differentiate the tumour from the nasopharyngeal activity.[18,24]

The results of the present study indicate that with a sensitive immunoperoxidase procedure the MoAbs 225·28S and Mel-14 show adequate binding in uveal melanoma tissue. The immunochemical study supports the results of some clinical studies indicating the usefulness of antibody 225·28S for immunodiagnostic procedures in uveal melanoma.[17,18] However in view of our clinical results as well as recent correspondence in this journal[25] the conditions of adequate immunoscintigraphy have to be carefully assessed.

A part of this study was presented at the International Symposium on Tumours of the Eye in Essen, West Germany, on 21–23 September 1989, organised by the German Ophthalmological Society (Deutsche Ophthalmologische Gesellschaft)

The authors thank Drs S Ferrone, New York Medical College, Valhalla, New York, S Carrel, Ludwig Institute for Cancer Research, Epalinges-sur-Lausanne, Switzerland, and C Figdor, The Netherlands Cancer Institute, Amsterdam, for kindly providing monoclonal antibodies 225 28S, Mel-14 and AMF-6, respectively We thank Drs E A van der Velde, Department of Medical Statistics, University Medical Centre Leiden for statistical computations, Mr F Kwaspen, Institute of Pathology, University Hospital Nijmegen, for technical assistance, and Mrs W J Baartse for editorial assistance

1 Kohler G, Milstein C Continuous cultures of fused cells secreting antibody of predefined specifity *Nature* 1975, 256: 495–7
2 Carrel S, Accolla RS, Carmagnole AL, Mach JP. Common human melanoma associated antigens detected by monoclonal antibodies. *Cancer Res* 1980; 40: 2523–8
3 Imai K, Molinaro GA, Ferrone S. Monoclonal antibodies to human melanoma associated antigens *Transplant Proc* 1980, 12: 380–3
4 Steplewski Z, Herlyn M, Herlyn D, Clark W, Koprowski H Reactivity of monoclonal anti-melanoma antibodies with melanoma cells freshly isolated from primary and metastatic melanoma. *Eur J Immunol* 1979, 9: 94–6
5 Hellstrom IH, Garrigues J, Cabasco L, Mosely GH, Brown JP, Hellstrom KE. Studies of a high molecular weight human melanoma-associated antigen. *J Immunol* 1983; 130: 1467–72.
6 Bumol TF, Reisfeld RA. Unique glycoprotein-proteoglycan complex defined by monoclonal antibody on human melanoma cells. *Proc Natl Acad Sci USA* 1982, 79: 1245–9
7 Brown JP, Woodbury RG, Hart CE, Hellstrom KE. Quantitative analysis of melanoma-associated antigen p97 in normal and neoplastic tissues *Proc Natl Acad Sci USA* 1981, 78: 539–43
8 Dippold WG, Lloyd KO, Li LTL, Ikeda H, Oettgen HF, Old LJ. Cell surface antigens of human malignant melanoma definition of six antigenic systems with mouse monoclonal antibodies. *Proc Natl Acad Sci USA* 1980; 77: 6114–8
9 Imai K, Natali PG, Kay NE, Wilson BS, Ferrone S Tissue distribution and molecular profile of a differentiation antigen detected by a monoclonal antibody (345·134S) produced against human melanoma cells. *Cancer Immunol Immunother* 1982; 12: 159–66.
10 Damato BE, Campbell AM, McGuire BJ, Lee WR, Foulds WS Monoclonal antibodies to human primary uveal melanomas demonstrate tumor heterogeneity *Invest Ophthalmol Vis Sci* 1986; 27: 1362–7.
11 Folberg R, Donoso LA, Atkinson BF, Ernst CS, Herlyn M, Arbizzon VV. An antimelanoma monoclonal antibody and the histopathology of uveal melanomas. *Arch Ophthalmol* 1985; 103: 275–9.

12 Van der Pol JP, Jager MJ, de Wolff-Rouendaal D, Ringens PJ, Vennegoor C, Ruiter DJ. Heterogenous expression of melanoma-associated antigens in uveal melanomas. *Curr Eye Res* 1987; 6: 757–65.

13 Bomanji J, Garner A, Prasad J, *et al.* Characterisation of ocular melanoma with cutaneous melanoma antibodies. *Br J Ophthalmol* 1987, 71: 647–50.

14 Wilson BS, Imai K, Natali PG, Ferrone S. Distribution and molecular characterization of a cell-surface and a cytoplasmic antigen detectable in human melanoma cells with monoclonal antibodies *Int J Cancer* 1981; 28: 293–300.

15 Natali PG, Bigotti A, Cavaliere R, Nicotra MR, Ferrone S. Phenotyping of lesions of melanocyte origin with monoclonal antibodies to melanoma-associated antigens and to HLA antigens. *J Natl Cancer Inst* 1984; 73: 13–24.

16 Natali PG, Bigotti A, Nicotra MR, *et al.* Analysis of the antigenic profile of uveal melanoma lesions with anti-cutaneous melanoma-associated antigen and anti-HLA monoclonal antibodies *Cancer Res* 1989; 49: 1269–74.

17 Bomanji J, Hungerford JL, Granowska M, Britton KE. Radioimmunoscintigraphy of ocular melanoma with ^{99m}Tc labelled cutaneous melanoma antibody fragments *Br J Ophthalmol* 1987; 71: 651–8.

18 Scheidauer K, Markl A, Leinsinger G, *et al* Immunoscintigraphy in intraocular malignant melanoma *Nucl Med Comm* 1988, 9: 669–79.

19 Schaling DF, Van Kroonenburg MJPG, Borsje RA, *et al* Radioimmunoscintigraphy with melanoma associated monoclonal antibody fragments in ocular melanoma *Graefes Arch Clin Exp Ophthalmol* 1989, 227: 291–4

20 Ruiter DJ, Bergman W, Welvaart K, *et al.* Immunohistochemical analysis of malignant melanomas and nevocellular nevi with monoclonal antibodies to distinct monomorphic determinants of HLA antigens *Cancer Res* 1984; 44: 3930–5.

21 Schlingemann RO, Rietveld FJR, De Waal RMW, Ferrone S, Ruiter DJ. Does the melanoma-associated high-molecular-weight antigen play a role in pericyte function during tumor angiogenesis? *Proc Am Assoc Cancer Res* 1989; 30: 378.

22 Ringens PJ, Van Haperen R, Vennegoor C, *et al.* Monoclonal antibodies in detection of choroidal melanoma *Grefels Arch Clin Exp Ophthalmol* 1989, 227: 287–90.

23 Siccardi AG, Buraggi GL, Callegaro L, *et al.* Multicenter study of immunoscintigraphy with radiolabelled monoclonal antibodies in patients with melanoma *Cancer Res* 1986; 46: 4817–22.

24 Bomanji J, Nimmon CC, Hungerford JL, Solanski K, Granowska M, Britton KE. Ocular radioimmunoscintigraphy: sensitivity and practical considerations. *J Nucl Med* 1988; 29: 1038–44.

25 Tullo AB, Dodd CJ, Noble JL, Owens S, Rao H Correspondence on ocular melanoma. *Br J Ophthalmol* 1989; 73: 771. Hungerford J In reply. *Br J Ophthalmol* 1989, 73: 771–2

British Journal of Ophthalmology, 1990, 74, 542–544

Congenital eyelid retraction

J R O Collin, L Allen, S Castronuovo

Abstract

Twenty two patients with primary congenital lid retraction affecting either the upper or lower eyelids or both are presented. The clinical features and management are discussed in the hope that recognition of this clinical entity will prevent unnecessary investigation.

Eyelid retraction is usually secondary to thyroid disorders, trauma, proptosis, seventh nerve palsy, or neurological abnormalities affecting the third nerve. Primary congenital lid retraction has been described only relatively rarely as individual case reports.[1-6] It is not well recognised as a clinical entity, and so individual patients may be investigated unnecessarily and the diagnosis not considered.[7] This report reviews the findings in 22 patients with congenital lid retraction affecting either the upper or lower eyelid.

Patients and methods

Twenty two patients with congenital lid retraction were examined over a 10-year period. To be included in this series as a case of upper lid retraction the upper lid had to be above the limbus on the affected side with a difference of at least 1½ mm between the upper eyelid levels on the two sides. The contralateral upper lid had to cover the limbus by not more than 1½–2 mm with the eyes in the primary position of gaze to avoid a potential diagnosis of contralateral ptosis. For lower lid retraction the affected lower lid had to be more than 1½ mm below the lower limbus with the contralateral lower lid at the limbus in the primary position of gaze. There was no history of thyroid problems in any of the patients or their mothers. Pregnancy and childbirth had been normal so far as could be ascertained in 18 cases. There were four cases with a history of forceps delivery. There was no other history of trauma. There was no proptosis. Seventh nerve function was normal. The pupils were equal and there was no ocular motor palsy. In all cases only one side was affected. The findings on full ocular examination were normal, and there was no significant refractive error. No other systemic abnormalities were detected in 19 cases. One child had a congenital cleft palate. Two children had asthma.

In all cases the condition was present at birth and this was verified with photographs if the patient presented after infancy. Sixteen patients presented as children before the age of 10 and four between 10 and 25, the range being nine weeks to 50 years of age. The presenting symptom was cosmetic in 18 patients, the condition often being thought to be either a large eye or a contralateral ptosis. Four patients had symptoms of redness or soreness in the mornings when they woke up which required lubricants. There was a positive family history in only one case, with a father being said to have had a similar condition to his daughter, who was the patient. Only one patient had both upper and lower lid retraction.

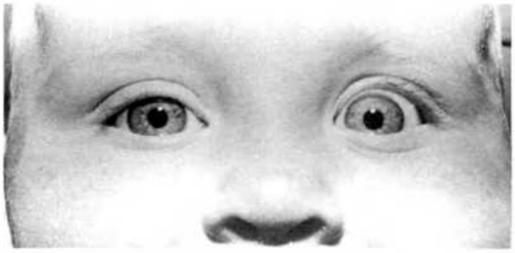


Figure 1: Congenital left upper lid retraction.

There were 19 cases with congenital upper lid retraction (Fig 1). The degree of lid retraction varied from 1½ to 5 mm average 3 mm. The levator function varied from 12 to 18 mm and was not significantly different from that on the contralateral side. The affected eyelid was definitely higher on extreme downgaze than the unaffected lid in at least 14 cases, and the rest were equivocal. The skin crease was the same height or lower than on the unaffected side in the majority of cases and was usually deeper, though this was difficult to measure quantitatively. Fourteen patients had normal binocular single vision with normal acuities and a full range of ocular movements. Three patients had a concomitant squint. This was an ipsilateral hypertropia with limitation of depression in two patients and an ipsilateral esotropia in one. In the first two cases the vision in the affected eye was normal, and in the third it was hand movements. Three patients had limitation of elevation on the involved side. Two patients had anisometropic amblyopia in the contralateral eye.

There were four cases with a congenital lower lid retraction (Fig 2). This varied from 2 to 4 mm, average 2·8 mm. The lower lid retractor function appeared normal, but it was not easy to get accurate measurements. There was limitation of elevation of the lower eyelid in full upgaze. The lower lid skin creases were marked. All cases had full binocular single vision with normal visual acuities and normal ocular movements.

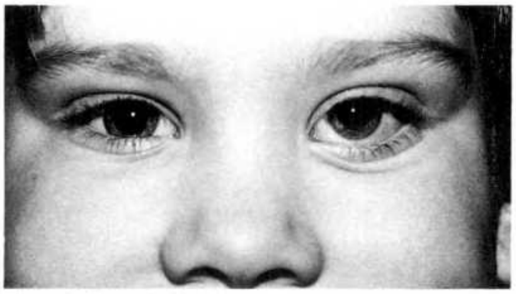


Figure 2: Congenital left lower lid retraction.

Moorfields Eye Hospital, City Road, London EC1V 2PD
J R O Collin
L Allen
S Castronuovo

Correspondence to:
J R O Collin, FRSC.

Accepted for publication 22 March 1990

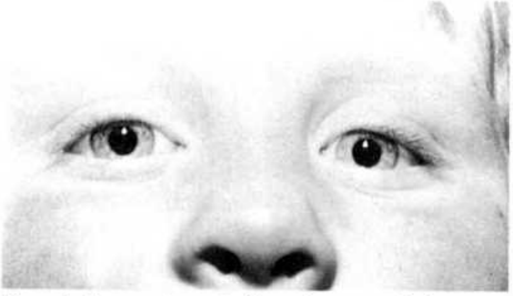


Figure 3: Same patient as in Figure 1 postoperatively.

All cases were observed for a minimum of one month (range one to 18 months). There was no change in the physical signs in any of the patients, and when they had not been seen early in life photographs and the subjective opinion of the patients and their families suggested that the condition had not changed. The indication for surgery in 15 patients was the cosmetic appearance of the upper or lower eyelid, and in only four cases was surgery performed because of symptoms of corneal exposure. If the patient presented as a child and was asymptomatic, the preferred age for surgery was around 4 years, when the child was aware of the defect and postoperative care was simplified.

At operation there was no gross limitation of movement of either the affected upper or lower eyelids on lid traction. An anterior approach was used initially to lower the upper lid in 11 patients and a posterior approach in five. Three patients did not undergo surgery. At operation the lid retractor complex appeared relatively normal, with a normal or thicker than normal levator muscle and aponeurosis but no obvious abnormality of the other eyelid structures. Routine light microscopy similarly did not show any gross abnormality, but one report did suggest that striated levator muscle fibres extended more anteriorly than usual. The lid was lowered with a z-myotomy or recession of the upper lid retractors, including Müller's muscle and the aponeurosis, with lysis of Whitnall's superior suspensory ligament of the globe as required. No scleral or other grafts were used. The lid was put on traction for 24-48 hours, and massage was used postoperatively if necessary to try to prevent the lid from rising too much.

Of the four patients with lower lid retraction all underwent surgery by the posterior approach. In two cases the lid was elevated by a recession of the lower lid retractors only, and two had a scleral graft interposed between the lower lid retractors and the lower border of the tarsus. The sclera was covered by mobilised conjunctiva. Postoperatively the lower lid was put on traction for 48 hours. No gross abnormality of any of the lower lid structures was detected at surgery.

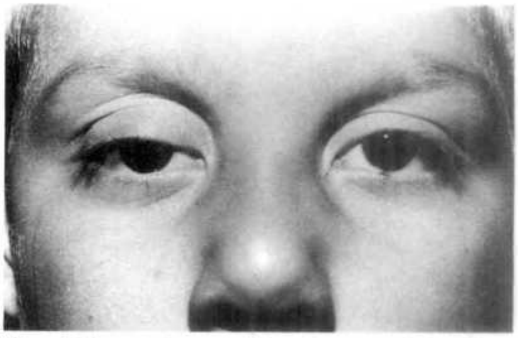


Figure 5: Same patient as in Figure 4 postoperatively with ptosis.

Results

Sixteen of the 19 patients with upper lid retraction underwent upper lid lowering. Twelve achieved a successful result (Fig 3), but in one patient the lid was too low and in three the lid was too high, with a difference of more than 1 mm between the upper lids. The patient whose lid was lowered excessively underwent subsequent ptosis surgery with a successful result (Figs 4, 5, 6). The three patients whose lids were not lowered adequately underwent a further upper lid lowering procedure with a successful result in two. One is waiting for further surgery when older.

All four of the patients with lower lid retraction underwent lower lid raising and achieved a satisfactory result, with lid levels which were approximately equal (Fig 7). The follow-up time for the results of both upper and lower lid surgery varied from one month to 2·3 years, average 11·2 months.

Discussion

Primary congenital lid retraction is a distinct entity and does not appear to change with time. It can involve the upper or lower eyelids or both and can only be diagnosed after excluding the other causes of lid retraction. The majority of cases present because of abnormal appearance, and in this series only 20% had symptoms of corneal exposure. It seems reasonable to manage these patients initially with observation to confirm the diagnosis by ensuring that the condition remains stable. Extensive investigations are not required. Lubricants can be prescribed if there are symptoms of corneal exposure. Observation

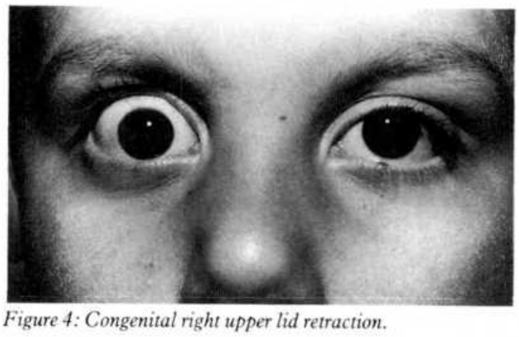


Figure 4: Congenital right upper lid retraction.

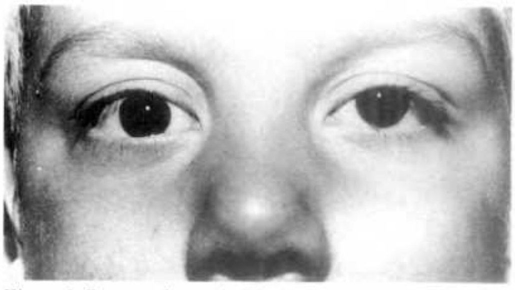


Figure 6: Same patient as in Figures 4 and 5 postoperatively after ptosis correction.

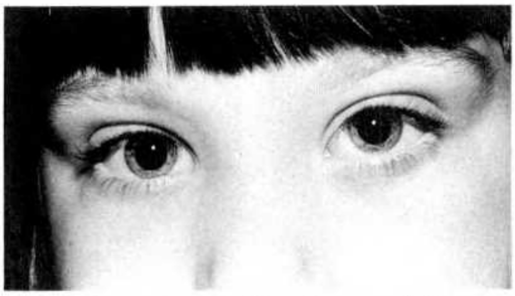


Figure 7: Same patient as in Figure 2 postoperatively.

includes orthoptic assessment, since three cases in this series did have squints, two of which were associated with amblyopia.

Eyelid retractor lengthening procedures are effective but the results are unpredictable (Figs 4-6). It is wise to delay surgery until the child is old enough to co-operate and to facilitate postoperative massage and so on which may be required to try to control the eyelid height. This usually means operating at about 4 years of age, but early surgery may be indicated if the child has symptoms of corneal exposure unrelieved by lubricants. The choice of an anterior or posterior approach to lower the lid depends on the height of the skin crease and the individual surgeon's preference. The skin crease will rise with a posterior approach retractor recession but theoretically can be controlled with an anterior approach procedure. Those patients with the greatest lid retraction all underwent an anterior approach upper lid retractor recession in an attempt to keep the skin crease equal in both upper eyelids. The posterior approach was used to correct the more minor degrees of lid retraction. The control of lid height and contour appeared better with the posterior approach, but this could have been because a lesser degree of change in eyelid level was being attempted. The predictability of eyelid lowering in this series would probably have been improved by delaying surgery until all the patients were old enough for local anaesthesia, but there was one adult whose result was unsatisfactory even after surgery under local anaesthesia. The results of upper lid retractor lengthening are variable in cases with other causes of lid retraction, such as thyroid eye disease, and there does not seem to be any particular way of reducing this unpredictability.[8]

The aetiology of the condition remains obscure. Examination of the eyelid tissues at operation did not show any obvious gross abnormality, though it did seem that the levator muscle fibres perhaps extended more anteriorly than usual and that the aponeurosis and orbital septum were particularly well formed as distinct layers. Routine histological examination confirmed the presence of normal looking, striated levator muscle fibres. The levator function in all these cases was good, but there was lagophthalmos on downgaze, which suggests that either the levator muscle or Müller's muscle did not relax properly. This might be due to an element of dystrophy, hypertrophy, or aberrant innervation of the muscle, or because the muscle, aponeurosis, or orbital septum was congenitally shorter and thicker than normal. It was not possible in this series to come to any more definitive conclusions about the aetiology, but our findings do show that the condition exists as an idiopathic, primary, benign entity, recognition of which may save patients unnecessary investigation.

This paper was presented in part to the American Society of Ophthalmic Plastic and Reconstructive Surgery in New Orleans on 28 October 1989.

1 Putterman AM, Urist M. Surgical treatment of upper eyelid retraction. *Arch Ophthalmol* 1972; **87:** 401–5.

2 Yee RD, Odeh-Nasrala N. Congenital, paradoxical retraction of the lower eyelid. *Am J Ophthalmol* 1974; **78:** 1027–9.

3 Baylis HI, Kamin DF. Correction of upper eyelid retraction. *Am J Ophthalmol* 1976; **82:** 790–4.

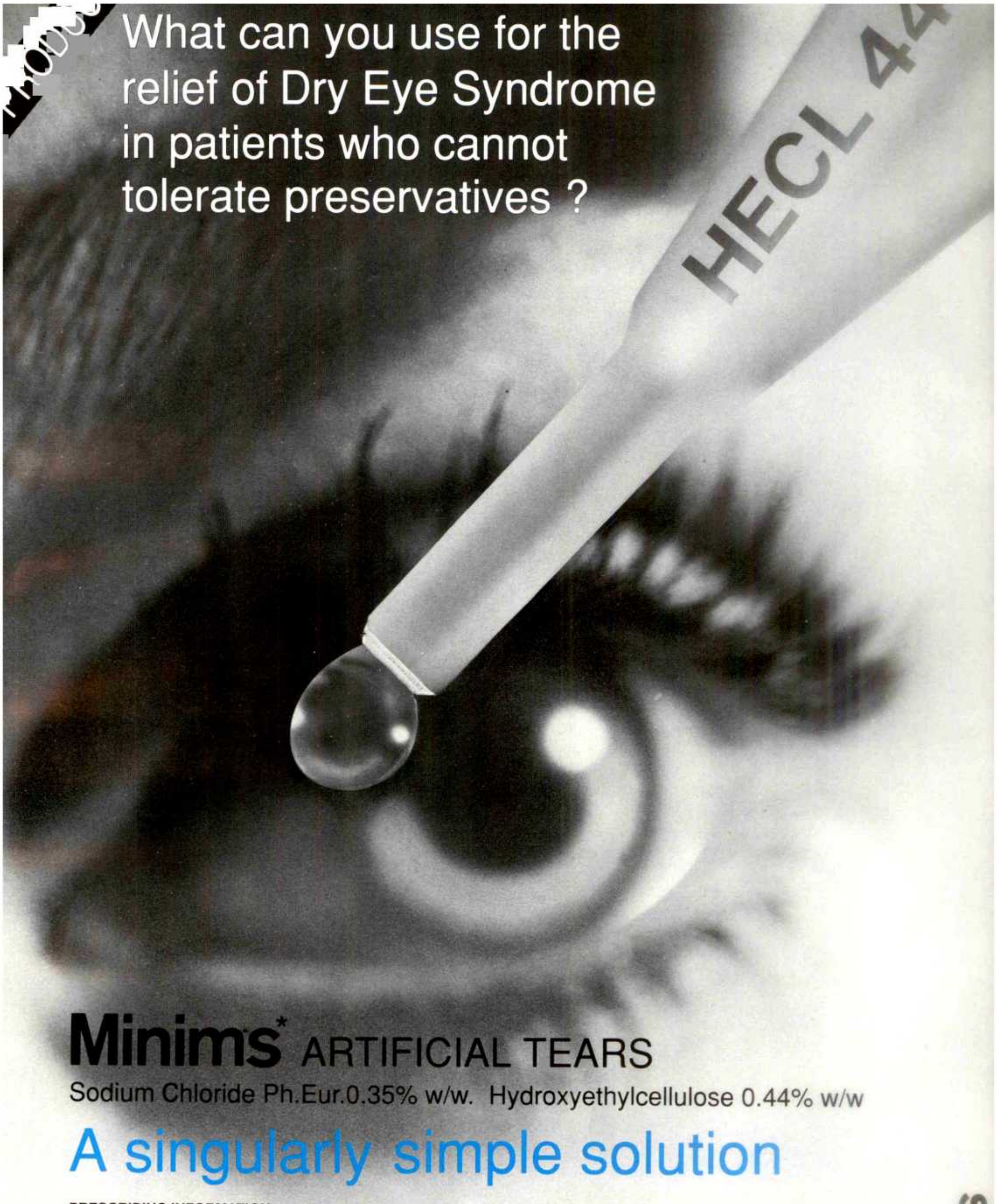
4 Leone CR Jr, Lewis R. Congenital upper eyelid retraction. *J Pediatr Ophthalmol Strabismus* 1976; **13:** 350–2.

5 Ballen PH, Rochkopf L. Congenital retraction of the upper lid. *Ophthalmic Surg* 1987; **18:** 689–90.

6 Rovit AJ, Deupree DM, Zang Y, Biglan AW. Treatment of congenital unilateral upper eyelid retraction with a marginal myotomy procedure. *Ophthalmic Surg* 1988; **19:** 872–5.

7 Sheilds CL, Nelson LB, Carpenter GC, Shields JA. Neonatal Graves' disease. *Br J Ophthalmol* 1988; **72:** 424–7.

8 Collin JRO. *A manual of systematic eyelid surgery* 2nd ed. London: Churchill Livingstone, 1989: 144–6.


What can you use for the relief of Dry Eye Syndrome in patients who cannot tolerate preservatives ?
HECL 44

Minims* ARTIFICIAL TEARS

Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

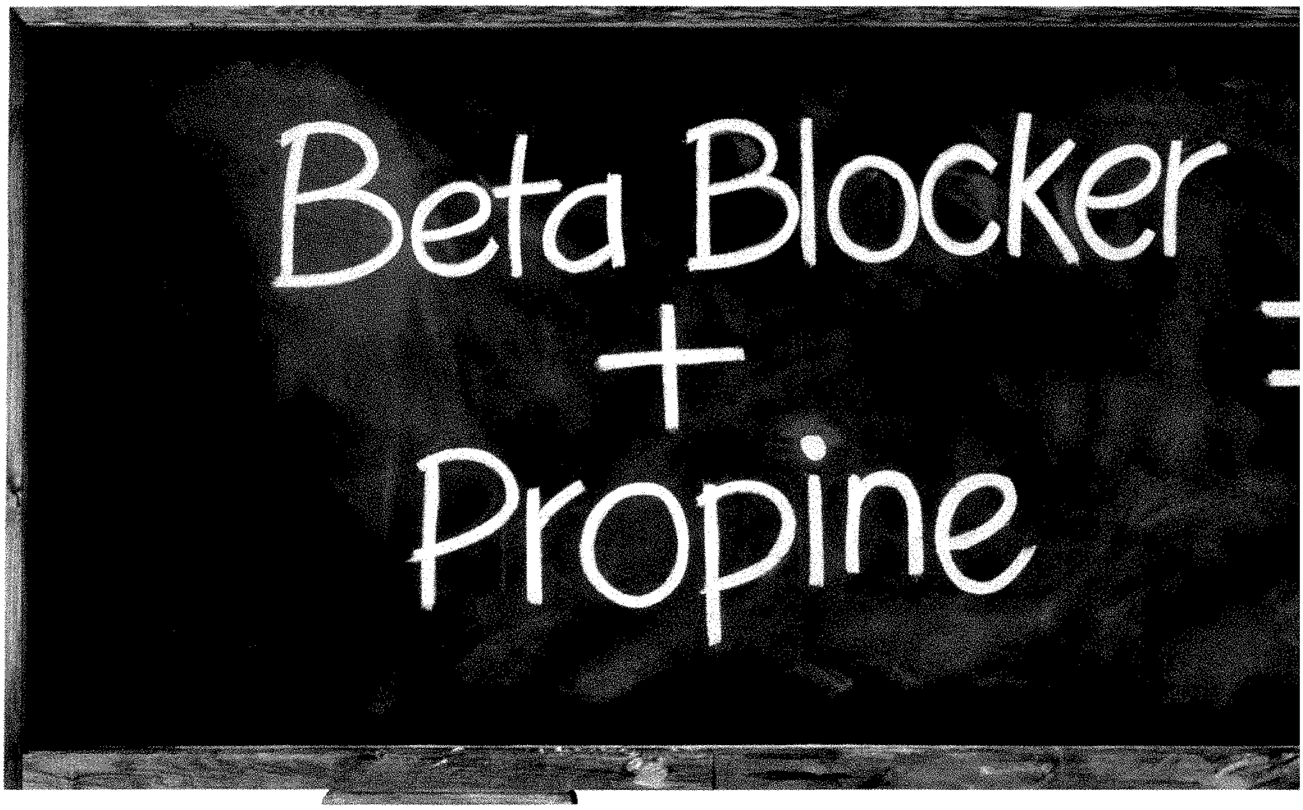
A singularly simple solution

PRESCRIBING INFORMATION
● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml. Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

* Trade Mark

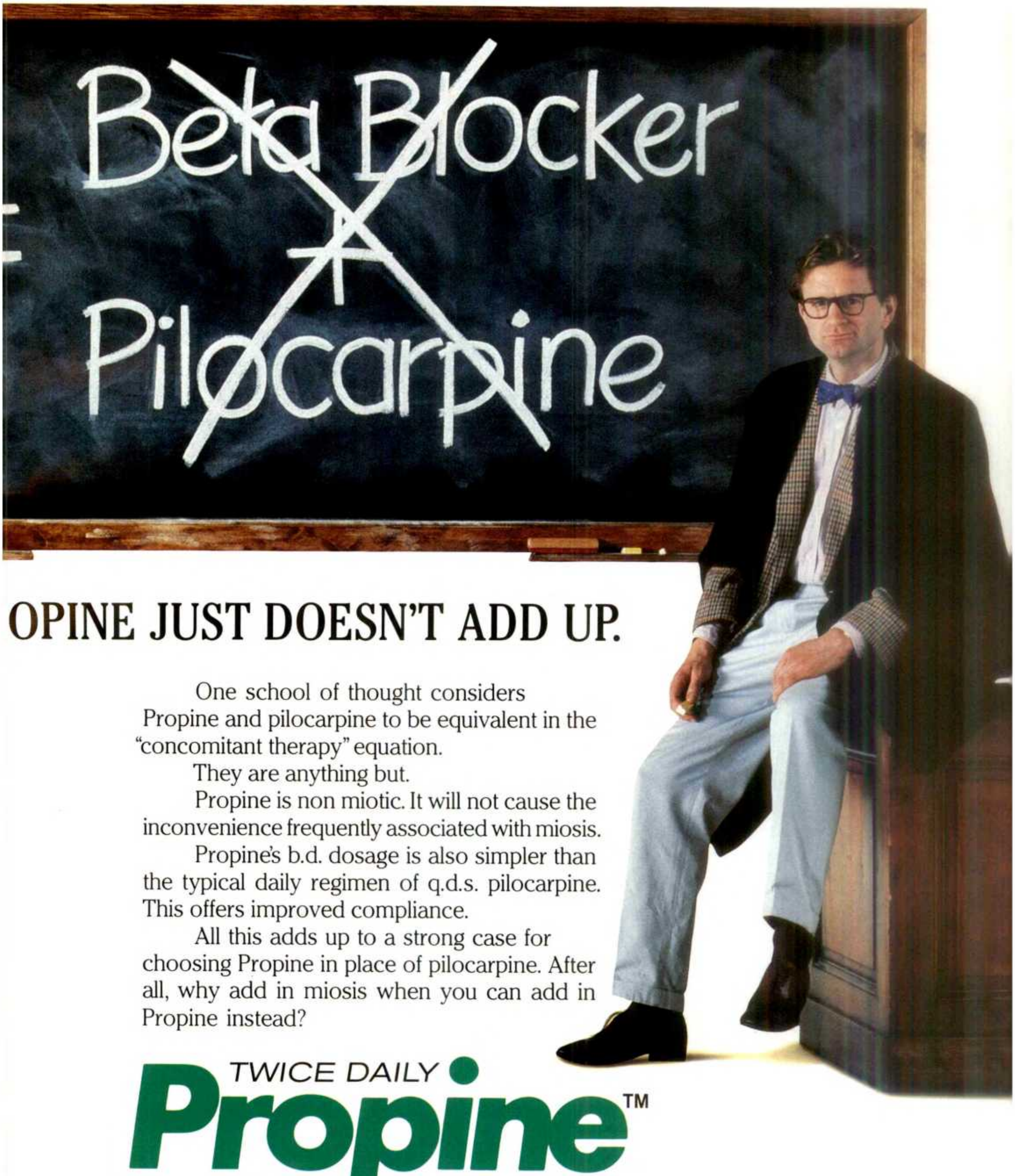
Smith+Nephew



EQUATING PILOCARPINE WI

PROPINE™ Prescribing Information

Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin
during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be
with caution in patients with narrow angles since dilation of the pupil may trig
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adre
use in aphakic patients. Prompt reversal generally follows discontinuance of the
Macular oedema with dipivefrin does present as a possibility in the aphakic patier
product contains benzalkonium chloride and should not be used by patients cont
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachy
arrhythmias and hypertension have been reported with ocular administrat



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY
Propine™
dipivefrin hydrochloride

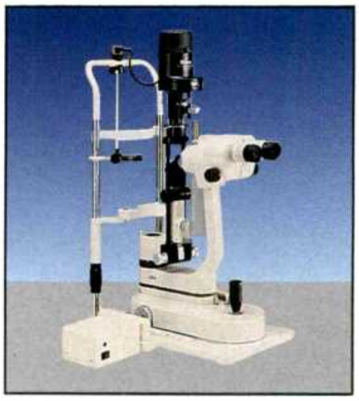
A CLEAR CHOICE IN THE GLAUCOMA EQUATION

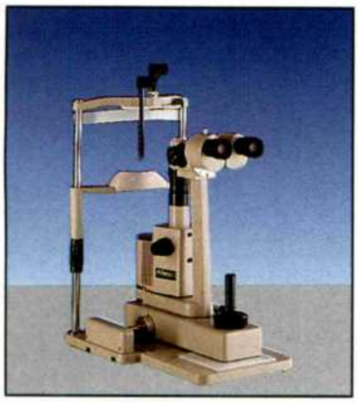
line, and may occur rarely with Propine therapy. Ocular: the most frequently
ed side-effects are conjunctival injection, and burning and stinging on instillation.
nd vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis,
een reported occasionally. Adrenochrome deposits in the conjunctiva and cornea
een associated rarely with use of dipivefrin. Follicular conjunctivitis has been
ed during long term therapy with Propine. The condition is reversible upon discon-
ce of the drug. **Pharmaceutical precautions** Store at room temperature. Discard
used contents 28 days after opening the bottle. **Legal category** POM. **Package**

quantities Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990.

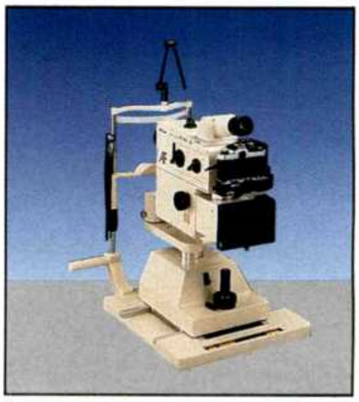
TM denotes trademark

ALLERGAN PHARMACEUTICALS





Why the Nikon Range stands up to any examination



Cast a critical eye over the Nikon range of ophthalmological equipment. A range which includes the clinical NS-1, CS-2 and research photo-slit FS-2 microscopes. Fault them if you can.

For quick and easy diagnosis, the Nikon NS-1, a new Goldmann type slit lamp, features a zoom magnification changer – total magnification range 5x – 71x. And, a high intensity 12V, 30W halogen lamp incorporating a special 'boost' switch enables brightness to be increased for short periods to minimise patient discomfort.

A powerful new addition to our range of aspherical lenses is a 90 diopter lens with a 60 degree viewing angle. Offering superior performance for fundus examinations, these lenses are designed to completely eliminate spherical aberration. Lenses available: 28D, 24D, 20D, 16D, 14D.

Our fundus cameras, NFC-50 and NFC-50AF, are designed for ease of operation. They boast the most advanced technology. Computer controlled functions; memory recall; autofocus and Nikon optics, of course.

There is no substitute for the best. And with Nikon nothing falls short of it. Our ophthalmological and optometric equipment proves that. But don't take our word for it – ask someone who cares about quality. Better still, make up your own mind.

Nikon

Nikon UK Limited, Instrument Division, Haybrook, Halesfield 9, Shropshire TF7 4EW. Tel: (0952) 587444

Please send me further information on Nikon Ophthalmological instruments. I am particularly interested in:

NS-1 ☐ CS-2 ☐ FS-2 ☐ NFC-50 ☐ Aspherical Lenses ☐

Name:________________

Title:________________

Company:________________

Address:________________

________________Tel:________________

British Journal of Ophthalmology, 1990, **74**, 545–550

The volume-deficient orbit: clinical characteristics, surgical management, and results after extraperiorbital implantation of Silastic block

Geoffrey E Rose, Harold Sigurdsson, Richard Collin

Abstract

The surgical techniques and results after extraperiorbital implantation of Silastic on the orbital floor of 70 patients are reviewed. In 11 patients the implant was through a subciliary approach and in 59 through an inferolateral cantholysis. The inferolateral cantholysis, a simplification of the McCord and Moses approach to the orbital floor, is particularly suited to this application. The implanted Silastic was retained in 66 patients, with an average follow up of 3·5 years (range <1 to 9·5 years), though six required surgery to debulk the anterior end of the implant. Further surgery was required in 27 patients, this generally being to correct the position of either the upper or the lower lid. Volume enhancement was effective in most cases, there being a significant reduction in the degree of recession of the prosthesis and the depth of the unsightly sunken sulci of the upper and lower lids. The mobility of the orbital contents, the prosthesis, and the upper lid was not improved.

After removal of the globe (about 7 ml) and associated soft-tissue loss (1–2 ml), there remains only about two-thirds of the original (27 ml) soft-tissue volume of the orbit. Together with fat atrophy secondary to the enucleation or to previous surgery or radiotherapy, the relative volume loss may be considerably more. Implantation of a large sclera covered acrylic ball[1-5] or an autogenous dermis-fat graft[3 5-8] replaces, at best, only 3–5 ml of this volume deficit. The orbit with a phthisical eye and fat atrophy has a soft-tissue volume similar to that of the anophthalmic socket with ball implant; throughout the rest of this paper the two will be considered as equivalent.

Whether the patient is anophthalmic or whether a residual globe is present (as phthisis), the volume deficient orbit has characteristic clinical features which may be considered to arise from one of three principal mechanisms, namely: (i) from inadequate tissue volume; (ii) from impaired orbital tissue movement; and (iii) secondary to previous treatments.

Moorfields Eye Hospital, London
G E Rose
H Sigurdsson
R Collin

Correspondence to:
Mr G E Rose, FRCS,
Moorfields Eye Hospital, City Road, London EC1V 2PD.

Accepted for publication
10 April 1990

CLINICAL CHARACTERISTICS OF THE VOLUME DEFICIENT ORBIT

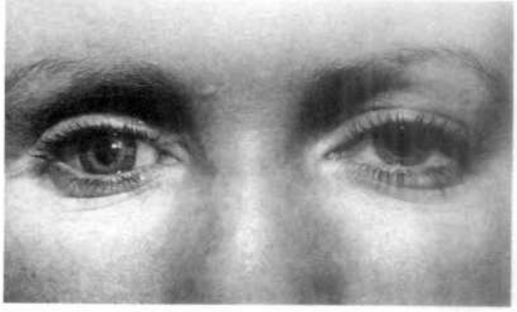


Figure 1a

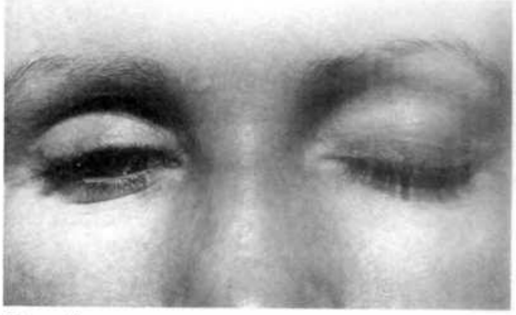


Figure 1b

Figure 1: Characteristic volume deficient right socket; with (a) marked recession of prosthesis and deeply sunken upper lid sulcus and (b) lagophthalmos due to over-sized prosthesis.

Inadequate soft-tissue volume produces the characteristic clinical signs of volume deficiency. These are a recessed prosthesis (for ease, termed 'enophthalmos') and a deeply sunken upper lid sulcus (Fig 1, 2a). The upper lid sulcus, normally filled out by the pressure of orbital fat, becomes hollowed from the effect of gravity on the inadequate residual orbital tissues. This effect of gravity is often exacerbated by an oversized prosthesis.

Owing to a foreshortening of the rectus muscles and the levator palpebrae complex recession of a sclera covered ball or phthisical eye into a volume deficient socket might be expected to reduce the mechanical efficiency of these muscles (Fig 2a), such loss of mechanical efficiency being manifest as poor mobility of the orbital contents and the prosthesis and as poor levator function (Figs 1a, b). Poor movement of the upper lid and the artificial eye promotes deposition and drying of mucus on the prosthesis. This frequently causes discomfort and discharge from the socket (Fig 3).

Correction of volume deficiency by the use of an over-large prosthesis causes several problems. A large artificial eye typically has poor stability and poor mobility. Such poor mobility, together with the large surface area of a big prosthesis, may contribute to the development of giant papillary conjunctivitis and chronic discharge (Figure 3). Lower lid laxity, due to the weight of a large prosthesis, may predispose to a spontaneous subluxation of the artificial eye. Furthermore, a large prosthesis may prevent

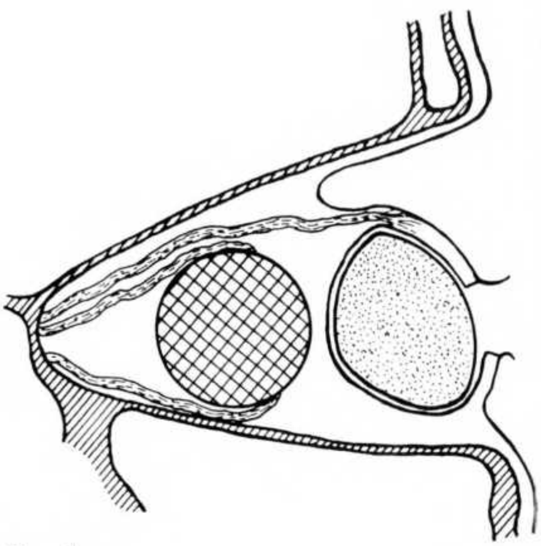


Figure 2a

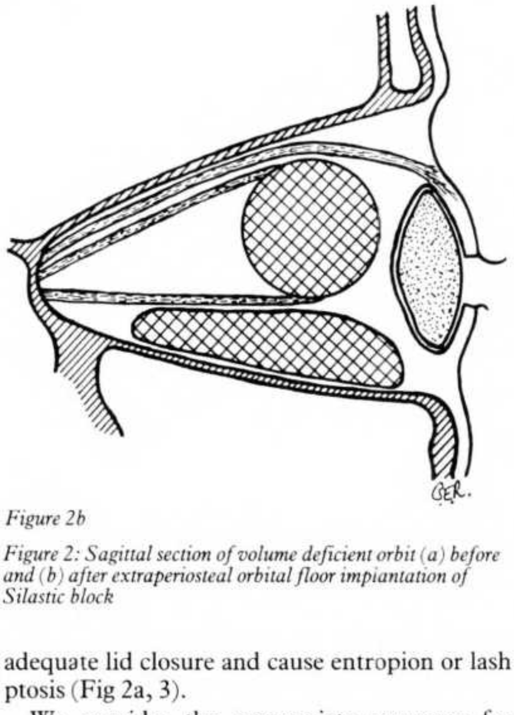


Figure 2b

Figure 2: Sagittal section of volume deficient orbit (a) before and (b) after extraperiosteal orbital floor implantation of Silastic block

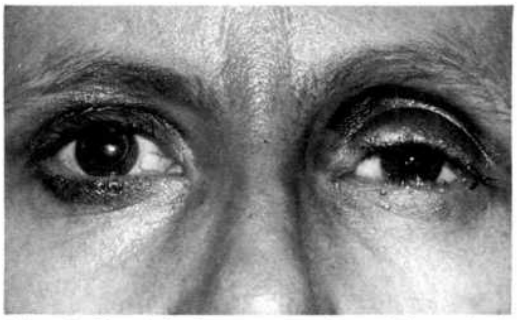


Figure 3: Chronic discharge, ptosis and upper lid entropion in a volume deficient socket.

adequate lid closure and cause entropion or lash ptosis (Fig 2a, 3).

We consider the appropriate sequence for treatment of the volume deficient orbit to be a restoration of adequate lining and enhancement of the volume of intraperiorbital contents (by dermis-fat graft or sclera covered acrylic ball), followed by an implantation of materials into the extraperiorbital space.[5] This paper reports the techniques and results of extraperiorbital implantation of Silastic block on to the orbital floor in volume deficient orbits.

Surgical methods and patient characteristics

The extraperiorbital space on the orbital floor may be reached either directly over the inferior orbital rim, by skin incision in the nasojugal fold,[9] or indirectly through a subciliary skin incision[10] or a lateral cantholysis combined with division of lower forniceal conjunctiva.[11]

For the present work we have simplified the approach of McCord and Moses.[11] In 59 patients the lateral end of the lower lid was divided, as a single layer, by means of scissors directed inferolaterally onto the orbital rim – an access that we term 'inferolateral cantholysis'. This simplified approach avoids the disinsertion of lower lid retractors and the division of lower forniceal conjunctiva that occurs with the approach of McCord and Moses.[11]

The nasojugal, subciliary, and McCord and Moses approaches to the orbital floor allow an incision of periosteum just within or just below the orbital rim and a direct view of the floor and any associated fractures. The anterior periosteal incision may, however, allow anterior migration of implanted materials, and these should therefore be fixed to the bone of the orbital rim.[9,10] In those patients of the present series who received implants under general anaesthesia through a subciliary approach a block of Silastic approximately 25×20×8 mm (Fig 4) was placed subperiosteally on the orbital floor and in most cases fixed with wire or nylon. The periosteal incision was then sutured thoroughly and the deep tissues and skin closed.

Inferolateral cantholysis is easy and provides adequate access to, but a poor view of, the orbital floor. This access is through a periosteal incision along the inferolateral rim of the orbit (Figure 5a). With a blunt dissector the periosteum was separated over the inferolateral part of the orbit and over the orbital floor. Although care was taken to avoid elevating periosteum along the anterior part of the orbital floor (Fig 5b), in later cases a wider band of intact periosteum was left. The silicone block, halved along its length, was then placed on the orbital floor in the correct orientation (Fig 6a) and the periosteum closed. A new lateral canthal tendon for the lower lid was fashioned from tarsal plate, this being affixed to a double ended suture attached to periorbita as far posterosuperiorly as could be reached inside the

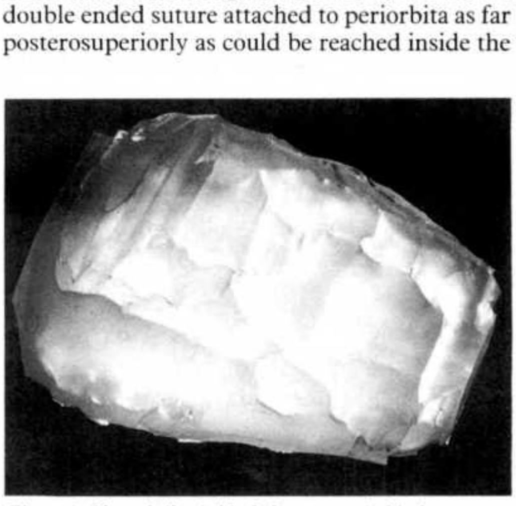


Figure 4: Shaped silastic block for extraperiorbital implantation on the orbital floor.

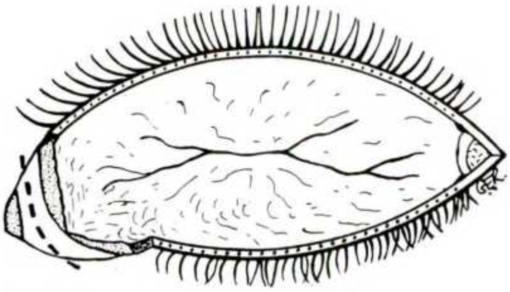


Figure 5a

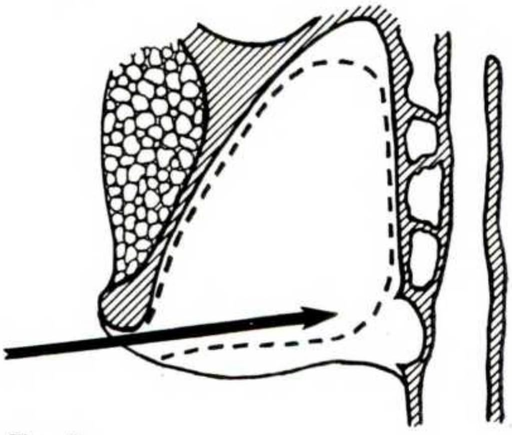


Figure 5b

Figure 5: Orbital floor implantation through an inferolateral cantholysis. (a) Position of periosteal incision and (b) extent of periosteal elevation across the orbital floor.

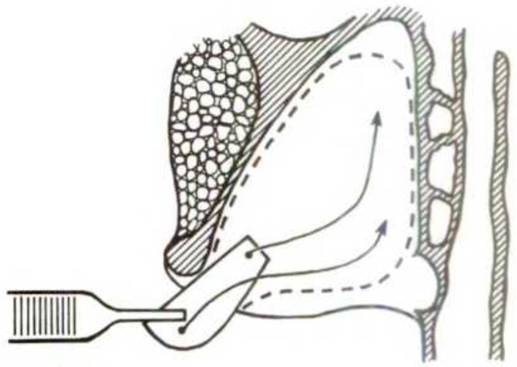


Figure 6a

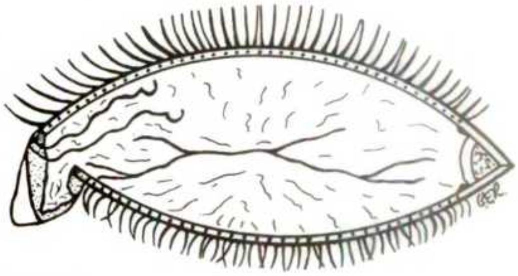


Figure 6b

Figure 6: Orbital floor implantation through an inferolateral cantholysis. (a) Single sweep manoeuvre for implantation and (b) refixation of the new lower limb for the lateral canthal tendon.

orbital rim (Fig 6b). The deep tissues and skin were then closed by standard techniques.

PATIENT CHARACTERISTICS

Seventy-eight patients underwent extraperiorbital implantation of Silastic block for volume deficient orbits, most between 1982 and 1989. Adequate preoperative and postoperative detail and follow-up were available for 70 of them.

The clinical characteristics of these patients were scored from 0 (minimum) to 3 (maximum), the score being based on details in the case notes or photographic records. Differences were assessed by use of the unpaired two-tail 'Student's' statistic or by the χ^2 statistic; a cautious interpretation of the latter is required because of small numbers in some samples.

Implantation was performed through an inferolateral cantholysis in 59 patients (84%; 19 male, 40 female) and by a subciliary approach in 11 (16%; 2 male, 9 female). The subciliary approach was used where the clinical history or radiological investigation suggested disruption of the orbital floor. Thus 6/11 (55%) of the subciliary patients had evidence of orbital floor fractures, in contrast to only 1/59 (2%) of the inferolateral cantholysis patients.

There were only minor differences between the patients having inferolateral cantholysis and those having a subciliary approach to implantation (Table I). The proportion of eyes enucleated for trauma was higher in the subciliary group, a result to be expected because of preoperative selection. The interval between the most recent surgery, namely intraperiorbital implantation of dermis-fat or acrylic, was significantly ($p<0{\cdot}05$) shorter for the patients having a subciliary approach. Although the range of follow-up after extraperiorbital implantation was similar for the two surgical techniques, the mean values were significantly ($p<0{\cdot}01$) different. This reflected the recently greater proportion in whom implantation was performed through an inferolateral cantholysis.

The presenting symptoms of the 70 patients are given in Table II.

Results

With both approaches to implantation of Silastic there was a significant reduction of 'enophthalmos' (cantholysis, $p<0{\cdot}001$; subciliary, $p<0{\cdot}01$) and of the depth of the upper lid ($p<0{\cdot}001$ and $p<0{\cdot}01$) and lower lid sulci ($p<0{\cdot}001$ and $p<0{\cdot}05$); the number of patients with each scoring is given in Table III.

Changes in the mobility of the orbital contents or the prosthesis were not significant with either surgical technique. Similarly, the depth of the fornices was unchanged and the stability of the prosthesis was unaffected by surgery (Table III). However, there was a significant improvement of lower lid laxity with the inferolateral cantholysis approach (scores 0 and 1 versus scores 2 and 3: $\chi^2=5{\cdot}47$, $p<0{\cdot}05$).

Although the mean palpebral apertures were similar on the affected and the unaffected side, both preoperatively and postoperatively, the range of values was somewhat greater on the affected side (Table IV). The latter reflected the variation, from ptosis to lid retraction, seen with volume deficient orbits. In comparison with normal eyes, however, preoperative levator function was reduced in volume deficient sockets (cantholysis, $p<0{\cdot}001$; subciliary, $p<0{\cdot}001$), and this abnormal function was not altered by extraperiorbital implantation of Silastic (Table IV). For patients where the position of the upper lid skin crease was recorded there was a significant reduction in the proportion with very high creases after orbital floor implantation through a cantholysis approach ($p<0{\cdot}001$; Table IV).

The complications of the procedure are listed in Table V, together with other surgery required. This surgery was often part of the planned treatment for the volume deficient orbit.

Discussion

Implantation of exogenous materials, such as Silastic block, into the extraperiorbital space on the orbital floor may add a further 3–5 ml to the orbital contents after a maximum enhancement of intraperiorbital volume.[3, 10–13] With only two exceptions all 63 patients in the present series who underwent enucleation had either dermis-fat (17) or acrylic (44) intraperiorbital implants prior to extraperiorbital implantation. One of the two exceptions later underwent implantation of a sclera covered ball for a persistent orbital volume deficiency.

Orbital floor implantation, readily performed through an inferolateral cantholysis, has the

TABLE I *Characteristics of patients undergoing orbital floor implantation of Silastic blocks*

	Surgical approach to implantation	
	Inferolateral cantholysis	*Subciliary blepharoplasty*
Total number	59	11
Reason for enucleation:		
Trauma	20	7
Neoplasm	13	0
Blind and painful eye	23	0
Not enucleated (phthisis)	3	4
Intraperiorbital implant:		
Acrylic	39/56 (70%)	5/7 (71%)
Dermis-fat	15/56 (27%)	2/7 (29%)
None	2/56 (3%)	–
Interval between intraperiorbital and extraperiorbital implantation (years):		
Mean	21·2	4·0
Standard deviation	19·1	5 0
Range	<1 to 38	1 to 15
Age at extraperiorbital implantation:		
Mean	40·3	29·6
Standard deviation	15·8	10·2
Range	17 to 78	20 to 49
Follow-up interval for extraperiorbital implants (years):		
Mean	3·2	5·4
Standard deviation	1·9	2·9
Range	<1 to 6·5	<1 to 9·5

TABLE II *Presenting symptoms for 70 patients with volume deficient orbits*

Symptom	*Frequency (incidence)*
Poor cosmesis	70 (100%)
Chronic discharge	24 (34%)
Unstable prosthesis	7 (10%)
Immobile prosthesis	4 (6%)
Malposition lower lid	4 (6%)
Ptosis	4 (6%)
Discomfort	4 (6%)

TABLE III *Preoperative and postoperative gradings for clinical signs; assessments are not available for all patients*

		Frequency in each clinical grade							
		Inferolateral cantholysis				*Subciliary blepharoplasty*			
Clinical sign	*Grade*	*0*	*1*	*2*	*3*	*0*	*1*	*2*	*3*
Enophthalmos	Pre	0	4	40	15	0	0	7	4
	Post	22	27	5	1	1	7	2	0
Deep upper lid sulcus	Pre	0	0	12	47	0	0	2	9
	Post	0	43	13	0	0	7	2	1
Deep lower lid sulcus	Pre	6	47	6	0	1	10	0	0
	Post	38	16	2	0	6	4	0	0
Depth upper fornix	Pre	0	0	9	50	0	0	2	9
	Post	0	0	8	48	0	0	2	8
Depth lower fornix	Pre	0	20	34	5	0	2	9	0
	Post	1	18	32	5	0	4	5	1
Lower lid laxity	Pre	24	10	14	8	4	3	1	1
	Post	27	16	5	5	4	2	2	1
Mobility of orbital contents	Pre	0	3	33	20	0	0	6	3
	Post	0	2	37	14	0	0	6	4
Mobility of prosthesis	Pre	1	22	34	1	0	2	7	0
	Post	1	13	41	1	0	2	6	1
Instability of prosthesis	Pre	30	18	9	1	6	2	1	0
	Post	27	16	6	7	5	2	3	0

Pre denotes preoperative assessments. Post denotes postoperative assessments.

TABLE IV *Changes in lid characteristics after Silastic implantation; assessments are not recorded for all patients*

Lid characteristic	*Surgical approach to implantation*			
	Inferolateral cantholysis		*Subciliary blepharoplasty*	
Mean, standard deviation (Number assessed)	*Unaffected side*	*Affected side*	*Unaffected side*	*Affected side*
Palpebral aperture (mm):				
Preoperative	9·4, 0·9 (36)	9·4, 2·0 (36)	9·1, 1 1 (7)	7·9, 1·7 (7)
Postoperative	9·6, 1·3 (31)	8·9, 1·9 (32)	9·3, 0·8 (6)	8·2, 1·6 (6)
Levator function (mm)				
Preoperative	15·1, 1·9 (34)	8·5, 3·2 (34)	15·6, 1·6 (8)	9·1, 3·2 (8)
Postoperative	14 6, 2·2 (14)	7·8, 2·8 (16)	15 5, 1·0 (4)	10·0, 1·6 (4)
Proportion with high upper lid skin crease (>10 mm):				
Preoperative	–	21/28 (75%)	–	3/6 (50%)
Postoperative	–	1/12 (8%)	–	2/4 (50%)

TABLE V *Complications of implantation and further surgical procedures*

	Surgical approach to implantation	
	Inferolateral cantholysis	*Subciliary blepharoplasty*
Complications of implantation:		
Migration of implant	13/59 (22%)	–
Infection of implant	1/59 (2%)	1/11 (10%)
Further surgical procedures:		
Removal of implant	3/59 (5%)	1/11 (10%)
Debulking of implant	6/59 (10%)	–
Upper lid surgery	13/59 (22%)	4/11 (36%)
Lateral canthal refixation	8/59 (14%)	3/11 (27%)
Lower fornix reformation	*11/59 (19%)	–

* Eight cases performed at the time of orbital floor implantation.

advantage that the intraperiorbital contents are not disrupted at operation, thereby reducing further orbital fat atrophy. The direct view of the orbital floor with the subciliary, McCord and Moses, or nasojugal approaches makes them the exposures of choice where there has been previous injury to the orbital floor.

The female preponderance in the present series (Table I) probably reflects a greater awareness of the cosmetic deformity of the volume deficient orbit among this sex; in all patients, however, the poor cosmesis was symptomatic (Table II). Orbital floor implantation appears to be well tolerated in adults at all ages and at a large range of times after previous surgery (Table I).

Extraperiorbital implantation of Silastic block produced a significant improvement in the cosmetic deformity due to lack of orbital contents; that is, in the 'enophthalmos' and the sunken upper and lower lid sulci (Figs 7a, b; Table III).

Although orbital floor implantation should enhance the mechanical efficiency of the rectus muscles and levator complex, by shifting the intraperiorbital contents anterosuperiorly and by allowing a smaller prosthesis to be fitted (Fig 2b), the present results show this not to be so (Table IV). In most cases the motility of the orbital contents and the prosthesis remained unchanged, and 17/70 patients (24%) required further surgery to correct the position of the upper lid.

Laxity of the lower lid was corrected in many cases where inferolateral cantholysis was used (Table III). However, in some of the earlier cases where either a soluble (4/0 polyglycolate) or an elastic (4/0 nylon) suture was used to reattach the canthal tendon, the lower lid subsequently became lax and required further reattachment. More recently 5/0 braided polyester has been used to refix the canthal tendon, and recurrent laxity of the lower lid is most unusual. Although the stability of the artificial eye appears to not be affected significantly by orbital floor implantation of Silastic (Table III), eight patients had a Silastic former for the lower fornix sutured to the periosteum at the time of surgery and three had lower fornix reformation as a secondary procedure (Table V). To allow a fitting of a stable prosthesis, seven implants that had migrated anteriorly after implantation through a cantholysis required debulking (six) or removal (one). We consider that the preservation, during the cantholysis approach to implantation, of a broader band of unstripped anterior periosteum (Fig 5b) has contributed to a reduced incidence of anterior migration of the Silastic blocks.

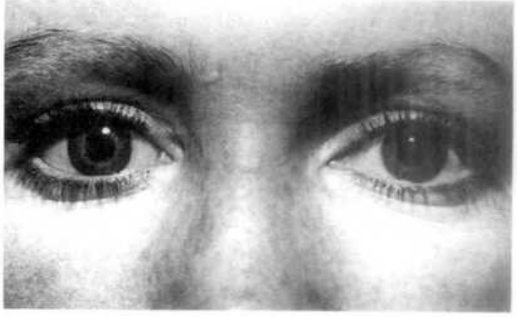


Figure 7a

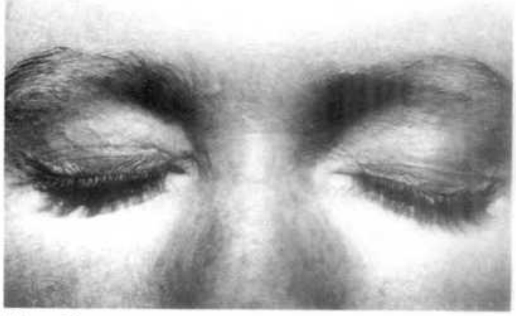


Figure 7b

Figure 7: Same patient as in Figure 1, but after orbital floor implantation of Silastic block; with eyes open (a) or closed (b).

For at least four weeks after surgery patients who have had cantholysis are advised to avoid using their old prosthesis, which is frequently too large. This veto reduces tension on the newly reconstructed lateral canthal fixation. During this period an acrylic former is kept in the socket. In accordance with the speed of resolution of postoperative swelling and bruising patients are then either fitted for a definitive artificial eye or their old prosthesis is reshaped and polished as a temporary measure.

Early postoperative complications were few. Transient postoperative infraorbital nerve hypoaesthesia was recorded in 15 cases, this probably being an underestimate of the true incidence of this complication. Swelling and bruising was considerable in some cases and were associated with moderate pain. However, in most cases postoperative pain was mild; only about one-half of all patients used simple analgesics and only about 15% required a single dose of opiate analgesia during the first two days after surgery.

An intravenous loading dose of a broad spectrum antibiotic was given to all patients at the time of surgery and an oral course continued postoperatively for seven to 10 days. One patient did not receive antibiotics; he developed a subperiosteal abscess and orbital cellulitis, this necessitating removal of the implant and drainage of the abscess. Another patient developed an extraperiorbital abscess six weeks after orbital floor implantation through a subciliary approach. It is possible, however, that previous orbital floor fracture in this patient predisposed to infection spreading from the maxillary antrum.

In addition to the two implants removed for infection and the one removed for anterior migration another patient insisted on removal for chronic late postoperative pain. The implant was therefore retained in 66/70 (94%) patients, with an average follow-up interval of 3·5 years (range 4 months to 9·5 years). The majority (81%) of patients were moderately (33/69) or very (23/69) satisfied with the results, though (13/69) were rather disappointed with the result.

1 Hervonet MF L'énucleation-éviscération *Bull Soc Ophtalmol Fr* 1958; 71: 508–13.

2 Frueh BR, Felker GV. Baseball implant. A method of secondary insertion of an intraorbital implant. *Arch Ophthalmol* 1976, 94: 429–30.

3 Soll DB The anophthalmic socket. *Ophthalmology* 1982; 89: 407–23

4 Tyers AG, Collin JRO. Orbital implants and post enucleation socket syndrome. *Trans Ophthalmol Soc UK* 1982; 102: 90–2

5 Collin JRO. *A manual of systematic eyelid surgery*. 2nd ed. Edinburgh: Churchill Livingstone, 1989: 121–33.

6 Smith B, Petrelli R Dermis-fat graft as a movable implant within the muscle cone *Am J Ophthalmol* 1978; 85: 62–6.

7 Smith B, Bosniak SL, Lisman RD. An autogenous kinetic dermis-fat orbital implant An updated technique. *Ophthalmology* 1982; 89: 1067–71.

8 Guberina C, Hornblass A, Meltzer MA, Soarez V, Smith B. Autogenous dermis-fat orbital implantation. *Arch Ophthalmol* 1983; 101: 1586–90

9 Soll DB Correction of the superior lid sulcus with subperiosteal implants *Arch Ophthalmol* 1971; 85; 188–90.

10 Spivey BE, Allen L, Stewart WB. Surgical correction of superior sulcus deformity occurring after enucleation. *Am J Ophthalmol* 1976; 82: 365–70.

11 McCord CD, Moses JL. Exposure of the inferior orbit with fornix incision and lateral canthotomy. *Ophthalmic Surg* 1979; 10: 53–63

12 Vistnes LM, Paris GL Uses of RTV silicone in orbital reconstruction. *Am J Ophthalmol* 1977; 83: 577–81.

13 Neuhaus RW, Shorr N. The use of room temperature vulcanizing silicone in anophthalmic enophthalmos *Am J Ophthalmol* 1982; 94: 408–11

THE SECOND MEDICO-LEGAL CONFERENCE
OF ACCIDENTS AND NEGLIGENCE
IN OPHTHALMOLOGY AND OTOLARYNGOLOGY

AUTUMN 1991

CALL FOR PAPERS

A section for Free Papers on medico-legal aspects of surgery will be included at the next Medico-legal Conference.

Papers can be on any aspect of medicine and the law However, priority will be given to papers which have a relevance to ENT and Eye surgery

A prize worth £150 will be given to the authors of the best paper, as judged by the Organising Committee

CLOSING DATE FOR FREE PAPERS
15th APRIL 1991

Papers should be submitted to

Mrs Janet Pye
Secretary/Research Assistant
Ear, Nose, Throat and Eye Research Foundation
North Riding Infirmary,
MIDDLESBROUGH
Cleveland TS1 4BR

and further details may be obtained by telephoning 0642 232323

Tennent Institute of Ophthalmology
University of Glasgow, Western Infirmary
38 Church Street, Glasgow G11 6NT

FULL-TIME POSTGRADUATE COURSES
IN OPHTHALMOLOGY
SEPTEMBER 1991 – JUNE 1992

These Courses cover clinical and surgical ophthalmology and related basic sciences (i.e. pathology, anatomy, physiology, pharmacology and optics) and include lectures, tutorials and practical refraction sessions. Students will also gain experience in the ophthalmic wards, out-patient clinics, casualty and operating theatre.

Courses are suitable for those preparing for higher qualifications in Ophthalmology (MCOphth, FCOphth, FRCS, and DO (Ireland).

Full details and application forms are available from the Professor of Ophthalmology at the above address.

UNIVERSITY OF LONDON

INSTITUTE OF OPHTHALMOLOGY

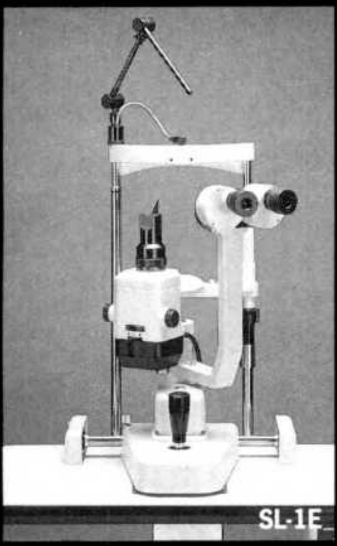
Associated with MOORFIELDS EYE HOSPITAL

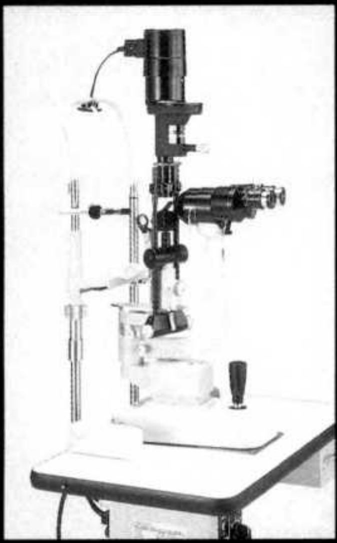
The following Courses have been planned:

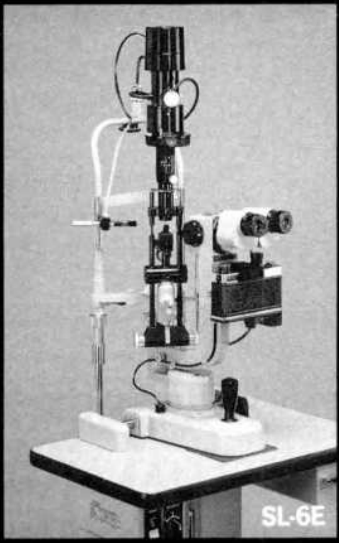
1990		
10th-28th September	FRCS Final Refresher Course	£400
3rd-5th October	Topics Symposia in Contact Lens Practice	£235
12th-16th November	General Practitioners Course	£200
19th-23rd November	Moorfields Macular Course	£325
3rd-21st December	MCOphth/DO Modular Refresher Course (per week) (3 modules of 1 week each)	£200 £550
1991		
14th-19th January	Paediatric Ophthalmology Course	£275
11th-15th March	General Practitioners Course	£200

Applications for all courses should be made to the

Dean's Office, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT







SL-1E
- 14mm slit illumination
- Omni directional joystick
- Variable magnification capability
- Built-in filters
- Halogen illumination

SL-2E
- Convergent binocular tubes enhance the examination
- Omni directional joystick
- Three-position magnification
- Infinitely adjustable slit width and length
- Built-in filters
- 35mm photographic attachment

SL-3E
- Omni directional joystick
- Two fixation targets
- Convenient, lever-controlled magnification change
- Slit beam inclination
- Four built-in filters
- Infinitely adjustable slit width and length
- Pachometer attachment

SL-6E
- Convergent binocular tubes for unprecedented viewing
- Omni directional joystick
- Five-position magnification
- Four built-in filters
- 35mm photographic attachments
- Polaroid attachment model PA-8S
- Video attachment
- Non-contact specular attachment
- Pachometer attachment
- Observation tube

In keeping with our philosophy of supplying only top quality equipment, Keeler are now the exclusive distributors for TOPCON.

The full range of Topcon slit lamps allows the practitioner to choose exactly the right instrument for his particular needs.

Within the range, Topcon now offers high magnification versions of their most popular slit lamps. These are illustrated opposite, and the details listed below.

If a permanent record is required, then this is achievable with photographic attachments which allow the use of 35mm, Polaroid or, in the case of the SL-6E, video recording.

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

LONDON CENTRE
Keeler Martin and Tomkins, 38 Margaret Street,
Cavendish Square, London W1A 4NS
Telephone: 01-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
Telephone: (0236) 721214 Fax: (0236) 721231

British Journal of Ophthalmology, 1990, 74, 551–555

Experimental *Acanthamoeba* keratitis: I. Preliminary findings

D F P Larkin, D L Easty

Abstract

Experimental *Acanthamoeba* keratitis was induced in Wistar rats by intrastromal inoculation of *Acanthamoeba polyphaga* cysts. Keratitis developed in all corneas injected and was characterised by a diffuse granular opacity. The animals were examined for 70 days and a gradual reduction of keratitis was observed. Pathological sections showed liquefactive stromal necrosis and *Acanthamoeba* localised in deep stroma persisting to 70 days. A brisk inflammatory infiltrate of neutrophils and macrophages was seen in the early days of infection. Severity of keratitis was found to correlate with inflammatory activity in pathological sections. The uses of an animal model of *Acanthamoeba* keratitis are described.

Acanthamoeba is a genus of free-living protozoon with a ubiquitous distribution in nature. It has a life cycle of active trophozoite and dormant cyst stages. First isolated and described in 1913,[1] it was not considered to have pathogenic potential until reported to cause fatal meningoencephalitis in animal inoculation experiments in 1959.[2] Some years later, when suspected amoebic encephalitis was reported in humans, the similarity to *Acanthamoeba* infection induced experimentally was recognised and suggested the aetiological role of *Acanthamoeba*. The pathological features of human encephalitis are so similar to those of experimental *Acanthamoeba* encephalitis in mice that the use of animal models for studying other forms of *Acanthamoeba* infection is clearly indicated.[3]

After initial reports[4 5] *Acanthamoeba* infection of the cornea remained a rare disease until an association with contact lens wear was first recognised.[6] Reports of cases have exponentially increased since that time, and a recent analysis identified 85% of affected patients as contact lens wearers.[7] *Acanthamoeba* keratitis typically has an indolent but progressive course, with intense discomfort and stromal infiltration. Therapy of *Acanthamoeba* keratitis is difficult in all cases, with frequent failures of medical and surgical treatment and loss of the eye in some of these.

Even though the keratitis has become more common than the encephalitis, few laboratory in-vivo studies have been reported. Rabbit models have been developed, first by Font and colleagues.[8 9] After subconjunctival administration of corticosteroid for four days the direct intrastromal injection of *A polyphaga* induced stromal keratitis and corneal ulceration. Some corneas were culture-positive at intervals, and encysted amoebae were observed in tissue on microscopy. A further rabbit model was reported by Lin and colleagues in which the effect of steroid administration was analysed.[10] Badenoch *et al* reported a model in Porton rats in which induction of *Acanthamoeba* keratitis was dependent on coinoculation with bacteria.[11]

In this study the Wistar rat was used as the experimental animal. The initial objective of the study was to induce reproducible disease similar to the human disease, for use in evaluation of immunopathology and therapeutic agents. So that the specific immune response to *Acanthamoeba* could be studied coinoculation with bacteria was avoided.

Materials and methods

Animals. Male Wistar rats weighing approximately 125 g were used. The corneas were examined prior to inoculation to exclude abnormality (Fig 1A). There were 24 rats in the infected group and six in the control group. All procedures were performed on the right eye.

Amoeba. All studies were performed with the Shinh strain of *A polyphaga*, a human corneal isolate (kindly provided by Mr S Kilvington, Public Health Laboratory, Bath). This had been frozen in liquid nitrogen and passaged on a Vero cell monolayer three times. An axenic suspension of 1×10^6 amoebae/ml (90% cysts) was prepared in Page's amoeba saline.[12]

Anaesthesia. Diazepam 0·25 mg and fentanyl 0·01 mg/fluanisone 0·3 mg were given by intramuscular injection, and one drop of preservative-free benoxinate was applied to the right eye.

Inoculation technique. The procedure was performed under an operating microscope (OPMI 1 FC, Carl Zeiss Ltd). Initially a half thickness linear blade incision was made approximately 2 mm from the centre of the cornea. With a microlitre syringe (Hamilton Bonaduz AG) and a sterile 30 G needle (Becton-Dickinson & Co.), the needle was advanced from the incision through the lamellae of the stroma to the centre of the cornea. 1 μl was injected into the stroma. Control animals received a mock inoculum of 1 μl of Page's saline; infection animals received a suspension of 1×10^6 amoebae/ml (90% cysts) in Page's amoeba saline.

Clinical evaluation Under fentanyl general anaesthesia the rats were examined with a slit-lamp microscope on days 1, 3, 5 and 7 following inoculation and weekly therafter until 70 days. Examination was by retroillumination, resulting in transillumination of the albino iris and the cornea. The oblique slit beam was used to illuminate lesser degrees of opacity. A clinical grading system was used to describe corneal opacity:

Grade 3: opacity visible on retroillumination, obscuring iris vessel detail.

Department of Ophthalmology, Bristol Eye Hospital, Bristol
D F P Larkin
D L Easty

Correspondence to:
Mr D F P Larkin, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Accepted for publication 29 March 1990

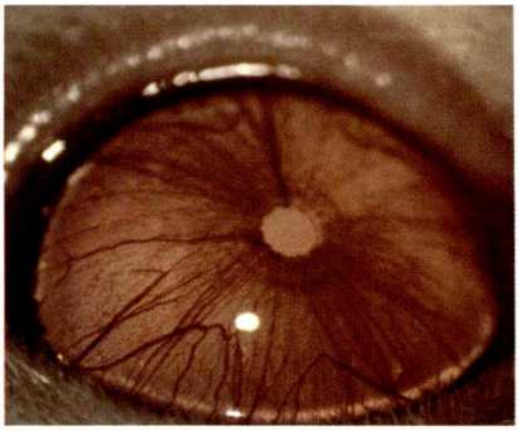


Figure 1A Normal rat cornea with transillumination of albino iris seen on retroillumination.

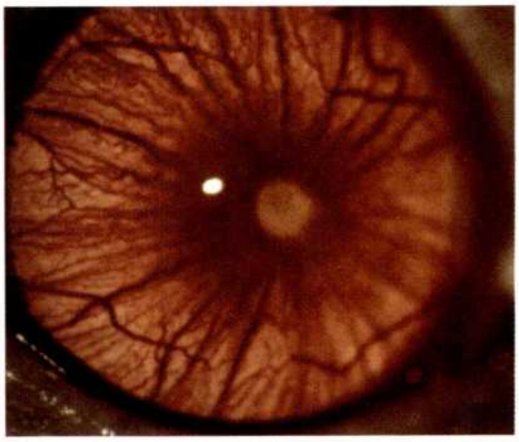


Figure 1B Day 5: infected rat cornea showing diffuse granular central corneal opacity.

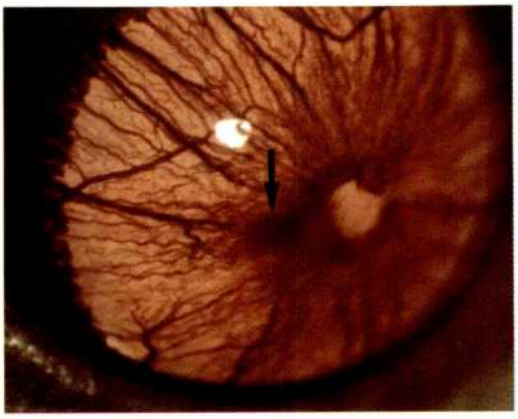


Figure 1C Day 14: clearance of much of the corneal oedema and maximal opacity at the inoculation site (arrow).

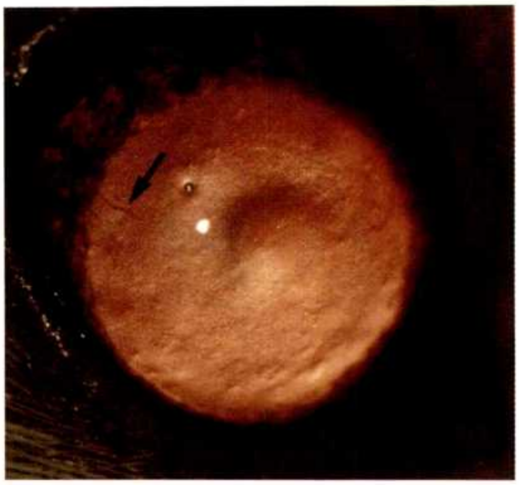


Figure 1D Day 35: paracentral ring-shaped granular opacity and fine superficial peripheral vascularisation (arrow), photographed following mydriatic administration.

Grade 2: opacity visible on retroillumination, but not sufficient to obscure iris vessels.

Grade 1: opacity visible only by oblique slit beam.

Grade 0: normal.

A mean opacity grade was calculated for the infected corneas on each examination day. Photographs were taken with the operating microscope with retroillumination of the cornea, 160 ASA tungsten film (Kodak Ektachrome) and automatic exposure.

On days 1, 3, 7, 14, 21, 28, 49, and 70 after inoculation two infected rats were killed by intraperitoneal injection of 60 mg pentobarbitone. Two control rats were killed on days 1, 3, and 7.

Tissue processing. The eye was enucleated and the cornea dissected from the globe and hemisected. One half of the cornea was fixed for 24 h in neutral buffered formaldehyde, embedded in wax, and 6 μm thickness sections cut with a microtome; the other half was either immediately frozen in liquid nitrogen or homogenised with a glass grinder for culture.

Preparation of specific antibody. Rabbit antiserum was prepared to the experimental strain of *A polyphaga* according to the method described by Warhurst.[13] Briefly, a 2·5 kg New Zealand White rabbit was injected intramuscularly with 30 ml *A polyphaga*/Freund's complete adjuvant and this was repeated at a three-week interval. This was followed by two 0·6 ml intravenous injections of formalinised *A polyphaga* cysts at four and five weeks. After venepuncture at six weeks the antiserum titre was measured and found to be 1/1024. The serum was then affinity purified on a chromatography column using protein A-Sepharose (Sepharose CL-4B, Pharmacia, Uppsala, Sweden) to yield the IgG fraction.[14]

Staining of wax sections. Sections were stained with haematoxylin and eosin or with rabbit anti-*Acanthamoeba* antibody. For the latter procedure sections were first incubated at room temperature with 1:5 normal swine serum (Dakopatts a/s) to block non-specific background staining; they were then incubated in sequence with rabbit anti-*Acanthamoeba* antibody at dilution 1:10 for 30 minutes, and peroxidase-conjugated swine anti-rabbit immunoglobulin (Dakopatts a/s) at dilution 1:50 for 30 minutes. Phosphate-buffered saline (PBS) was used for all dilutions, and sections were washed with PBS following each of these incubations. 3,3′-Diaminobenzidine (Sigma Chemical Co.) was the chromagen used to identify antibody binding, mixed with H_2O_2 in 0·1 M trometamol (Tris) buffer, giving a brown end-product: sections were incubated for three minutes and then washed in tap water for five minutes. Sections were counterstained with haematoxylin.

Culture of corneas for Acanthamoeba. Non-nutrient agar was set in each well of 25-well Petri plates. A lawn of live *Escherichia coli* was added to the agar surface in each well, and after 8 hours' incubation at 37°C the plates were ready for inoculation with tissue. Hemicorneas were homogenised in 150 μl of Page's saline with a glass grinder, 10 μl of the undiluted homogenate added to each well, and the plate sealed. Corneas from control and infected eyes were cultured and observed by microscopy for seven days. If no growth was seen by seven days, the culture was deemed negative.

Results

CLINICAL EVALUATION

The cloudy opacification observed immediately after injection of all corneas cleared completely in control rats before the first examination day 1. Reepithelialisation of the linear incision had also occurred by this time.

All rats inoculated with *Acanthamoeba* developed keratitis. Certain clinical features were consistently observed. Opacity was granular in character, with corneal thinning superficial to infiltrates apparent in animals with more longstanding keratitis. Minimal, if any, vascularisation and no corneal perforation was seen (Figs 1B, 1C, 1D). No epithelial disease and no signs of anterior uveitis such as nodular infiltrates or hypopyon were observed.

On days 1, 3, and 5 following inoculation grade 3 opacity was observed in almost all rats, maximal at the inoculation site. On day 7 corneal opacity was grade 3 in most rats but had diminished to grade 2 in some. On subsequent examinations a gradual reduction in mean grade of corneal opacity was found (Table I).

EXAMINATION OF PATHOLOGICAL SECTIONS

Haematoxylin and eosin (H-E) staining of infected corneas identified a marked inflammatory response of neutrophils and macrophages at the inoculation site on day 1 (Fig 2A). A distinction between *Acanthamoeba* and inflammatory cells was not possible by H-E stain but was facilitated by immunoperoxidase staining with anti-*Acanthamoeba* antibody (Fig 2B). Excystment of many amoebae (Fig 2C) and trophozoite migration from the inoculation site was seen by day 3. A more subdued and mixed inflammatory response was evident by this time, with lymphocytes and monocytes appearing among the neutrophils and macrophages seen on day 1. By day 7 trophozoites were seen throughout the cornea, though large numbers of cysts remained at the inoculation site. Marked stromal thinning was seen overlying the inoculation site in some corneas at day 14 (Fig 2E). Examination of corneas late in disease, from days 21 to 70, consistently revealed amoebae and inflammatory cells to be localised to the inoculation site, surrounded by eosinophilic material.

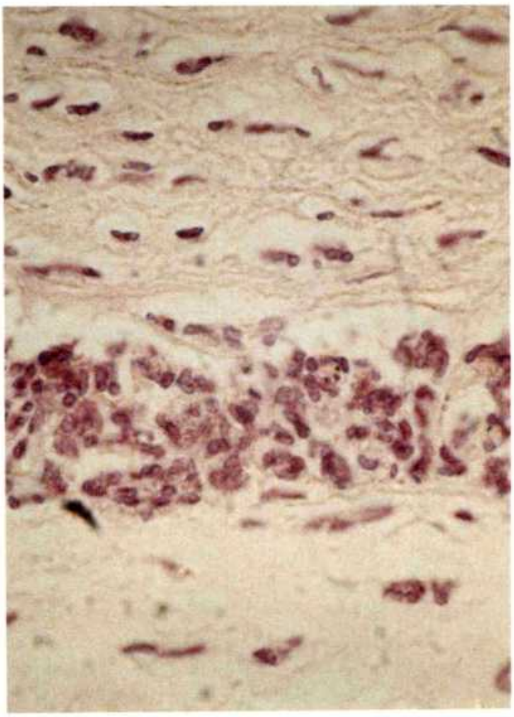


Figure 2A Day 1: non-specific staining by amoebae and inflammatory cells at the inoculation site in an infected cornea. (H-E, ×540.) They are very difficult to distinguish.

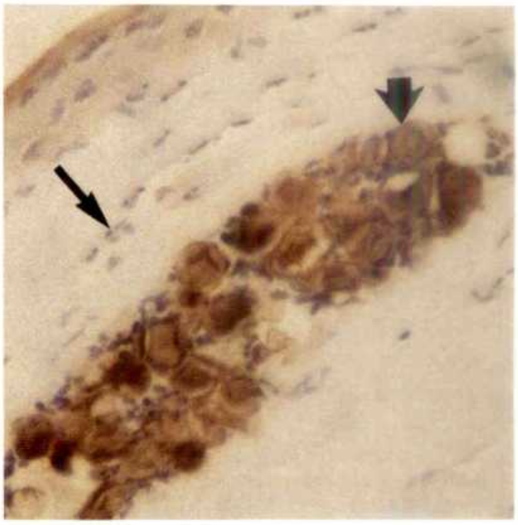


Figure 2B Day 1: Acanthamoeba *cysts (large arrow) and migrating polymorphs (small arrow). Little excystment has taken place. (Anti-* Acanthamoeba *antibody × 300).*

A gradually diminishing inflammatory response was seen in control corneas at 1, 3 and 7 days after mock inoculation (Fig 2F).

CULTURE OF CORNEA

Positive *Acanthamoeba* cultures resulted from infected corneas of all animals killed at days 1–49 inclusive. The homogenised corneas of the rat killed at day 70 and all control rats were culture-negative.

Discussion

The value of an animal model of *Acanthamoeba* keratitis is attested to by the gravity and increasing prevalence of clinical disease in humans. Study of *Acanthamoeba* keratitis in an animal model allows control of many of the variable factors involved in human disease. In

Table I Mean grade of keratitis observed following injection of Acanthamoeba

Day	*Number of rats examined*	*Mean grade of keratitis (SD)*
1	*24*	*2·72 (0·60)*
3	*22*	*2·76 (0·61)*
5	*20*	*2·77 (0·59)*
7	*18*	*2·42 (0·79)*
10	*16*	*2·08 (0·81)*
14	*14*	*1·75 (0·65)*
21	*12*	*1·71 (0·76)*
28	*10*	*1·93 (0·83)*
42	*8*	*1·29 (0·49)*
70	*6*	*1·50 (0·58)*

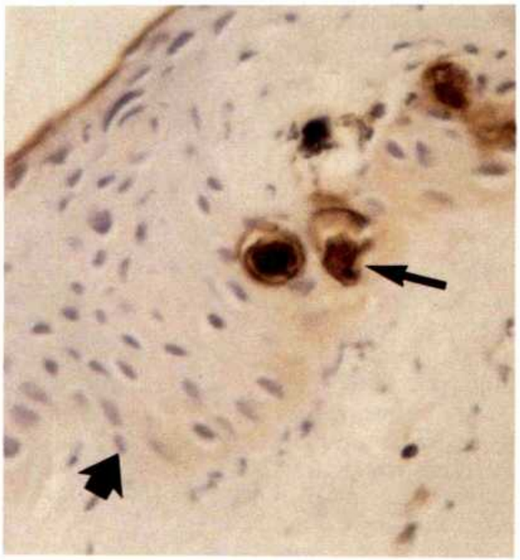


Figure 2C Day 1: excysting Acanthamoeba *(thin arrow) at the site of the linear blade incision, indicated by epithelial downgrowth (wide arrow).* Anti-Acanthamoeba *antibody, ×300.)*

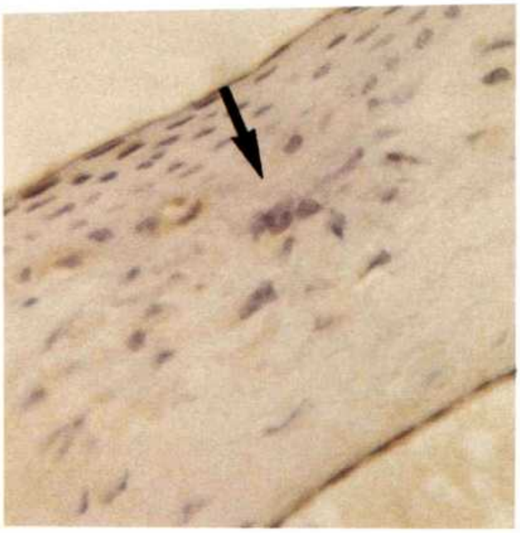


*Figure 2F Day 3: control cornea showing low-grade inflammation at inoculation site (arrow). (Anti-*Acanthamoeba *antibody, ×190.)*

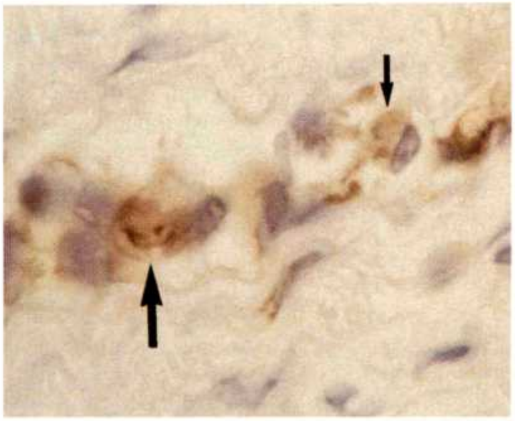


*Figure 2D Day 7: cyst (large arrow) and trophozite (small arrow), each being killed by several inflammatory cells (Anti-*Acanthamoeba *antibody, ×760.)*

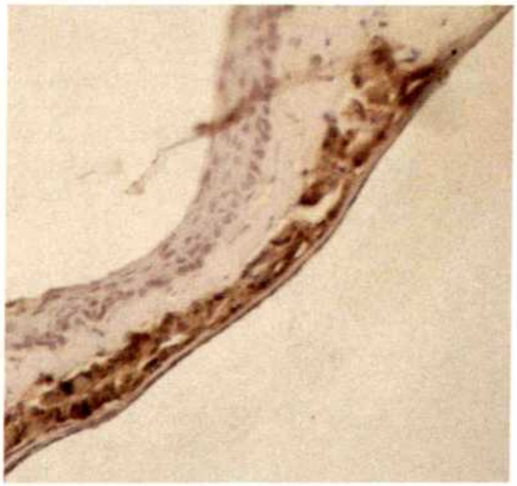


Figure 2E Day 14: marked thinning of corneal stroma overlying Acanthamoeba *cysts which are in deep stroma. These have not migrated and rest on Descemet's membrane. (Anti-*Acanthamoeba *antibody, ×140.)*

particular, the clinical features of established stromal infection may be analysed, pathological study of tissue undertaken, and, in an established model, treatments evaluated. The most appropriate treatment for *Acanthamoeba* keratitis has yet to be decided: insufficient correlation between in-vitro drug sensitivity tests and clinical response renders it difficult to evaluate new drugs.

In this study *Acanthamoeba* keratitis was induced by inoculation of organisms directly into the corneal stroma. Therefore this model does not address questions on the means by which infection arises, but what follows once a large number of cysts reach the stroma. Reproducible keratitis developed in all rat corneas inoculated with 1 μl of a suspension of *Acanthamoeba* at a concentration of 1×10^6/ml. Because in clinical practice such an inoculum of cysts would be very unlikely, this may indicate that *Acanthamoeba* are less infective for the rat cornea than the human. Certain clinical features mimic those observed in human infection, such as minimal corneal vascularisation and diffuse granular opacity formation rather than formation of an abscess. Although acute fulminating infection was not induced, the clinical course of the experimental keratitis is shorter than the human disease, which may remain active for several months. This might be due to differences in rat and human susceptibility to infection. In general, clinical inflammation correlated with histopathological indices of inflammation rather than presence of amoebae as such. In accordance with the report of Font *et al.*[9] cysts seemed more resistant to destruction than trophozoites.

Most human specimens on which histopathological descriptions are available originate from corneal transplantation and accordingly describe late stages of the disease, probably modified by drug therapy. Nevertheless, available reports describe changes similar to those described in this report. Disruption and necrosis of stromal lamellae and invasion by amoebae of deep stroma to Descemet's membrane are observed with infiltrates of neutrophils; in some cases there is an added lymphocyte and plasma cell component.[6 15-17] However, *Acanthamoeba* can be seen in tissue relatively free of inflammation.[17 18]

Initial conclusions from this study indicate that reproducible keratitis of short clinical duration can be induced by intrastromal injection of axenic *Acanthamoeba* cysts without the need for concomitant immunosuppression by corticosteroid[8-10] or coinoculation with bacteria.[11] Thus the rat provides a useful model for investigating the pathology of *Acanthamoeba* keratitis. Further sequential studies are in progress to characterise the cellular composition of the immune response to *Acanthamoeba*. This model will provide improved understanding of *Acanthamoeba*-host interactions and ultimately will allow evaluation of specific antimicrobial drugs with and without corticosteroid.

This study was supported in part by grants from Alcon Laboratories Ltd, the British Council for the Prevention of Blindness, and the South-Western Regional Health Authority.

The authors are indebted to Simon Kilvington, BSc, for initially providing *Acanthamoeba* cysts and assisting with preparation an anti-*Acanthamoeba* antibody; and to Ian Williams for assistance with the preparation of tissue sections.

1 Puschkarew BM. Über die Verbreitung der Susswasserprotozoen durch die Luft. *Arch Protistenk* 1913; 28: 323–62.
2 Culbertson CG, Smith JW, Cohen HK, Minner JR. Experimental infection of mice and monkeys by *Acanthamoeba*. *Am J Pathol* 1959; 35: 185–97
3 Martinez AJ. *Free-Living Amebas: Natural History, Prevention, Diagnosis, Pathology, and Treatment of Disease.* Boca Raton: CRC Press, 1985; 127–44
4 Jones DB, Visvesvara GS, Robinson NM. *Acanthamoeba polyphaga* keratitis and *Acanthamoeba* uveitis associated with fatal meningoencephalitis. *Trans Ophthalmol Soc UK* 1975; 95: 221–32.
5 Nagington J, Watson PG, Playfair TJ, McGill J, Jones BR, Steele ADMcG. Amoebic infection of the eye. *Lancet* 1974; ii: 1537–40.
6 Moore MB, McCulley JP, Luckenbach M, *et al.* *Acanthamoeba* keratitis associated with soft contact lenses. *Am J Ophthalmol* 1985; 100: 396–403.
7 Stehr-Green JK, Bailey TM, Visvesvara GS The epidemiology of *Acanthamoeba* keratitis in the United States. *Am J Ophthalmol* 1989; 107:331–6
8 Font RL, Tapert MJ, Robinson NM, Osato MS, Jones DB. An animal model of *Acanthamoeba* keratitis. *Invest Ophthalmol Vis Sci* 1981; 20 (suppl). 8.
9 Font RL, Tapert MJ, Robinson NM, *et al.* An animal model of *Acanthamoeba* keratitis. Further studies with emphasis on the early phase destruction of the trophozoites. *Invest Ophthalmol Vis Sci* 1982; 22 (suppl) 163.
10 Lin J, John T, Sahm D, Rockey JH. Animal model of *Acanthamoeba* keratitis: effect of corticosteroids *Invest Ophthalmol Vis Sci* 1989; 30: (suppl): 37.
11 Badenoch PR, Johnson AM, Christy PE, Coster DJ. Pathogenicity of *Acanthamoeba* and a corynebacterium in the rat cornea. *Arch Ophthalmol* 1990, 108: 107–12.
12 Page FC Taxonomic criteria for limax amoebae, with descriptions of 3 new species of *Hartmannella* and 3 of *Vahlkamphia*. *J Protozool* 1967; 14: 499–521
13 Warhurst DC *Naegleria* and *Acanthamoeba* in tissue sections. In: Edwards JMB, Taylor CED, Tomlinson AH, eds *Immunofluorescence techniques in diagnostic microbiology* London: HMSO, 1982; 46–8.
14 Tucker DF, Begent RHJ, Hogg NM Characterization of immune complexes in serum by adsorption on staphylococcal protein A: model studies and application to sera of rats bearing a Gross virus-induced lymphoma. *J Immunol* 1978, 121: 1644–51
15 Lund OE, Stefani FH, Dechant W Amoebic keratitis. a clinicopathological case report. *Br J Ophthalmol* 1978; 62: 373–5
16 Auran JD, Starr MB, Jakobiec FA, *Acanthamoeba* keratitis. A review of the literature. *Cornea* 1987; 6: 2–26.
17 Garner A. Pathology of corneal acanthamoebic infection. In: Cavanagh HD, ed. *The cornea: transactions of the World Congress on the Cornea III*. New York· Raven Press, 1988: 535–9.
18 Blackman HJ, Rao NA, Lemp MA, Visvesvara GS. *Acanthamoeba* keratitis successfully treated with penetrating keratoplasty suggested immunogenic mechanisms of action. *Cornea* 1984 3: 125–30.

British Journal of Ophthalmology, 1990, **74**, 556–558

Computerised visual field deficits in tears of the retinal pigment epithelium

Joseph I Maguire, William H Annesley Jr, William L Decker, Gary C Brown, David H Fischer, Joan M Slagle

Abstract

Retinal Pigment epithelial tears have been well documented as a complication of pigment epithelial detachment in patients with age related macular degeneration. Spontaneous and iatrogenic separation of detached retinal pigment epithelium, with subsequent retraction and exposure of the underlying choriocapillaris and Bruch's membrane, usually results in poor visual function in the affected areas. However, exact characterisation of the resultant scotomas has not been previously described. We present two patients with spontaneous pigment epithelial tears who underwent Octopus computerised visual field analysis. The density and characteristics of their associated field loss is compared with their clinical and fluorescein angiographic appearance.

Retinal pigment epithelial tears or rips were first described by Hoskin *et al*[1] in 1981 as a newly recognised complication of age related macular degeneration in patients with associated pigment epithelial detachments. Several authors have since reported on this phenomenon.[2-7] Associated visual loss is usually abrupt and severe when the foveal or parafoveal area is involved.[1-6] Casswell and associates[5] noted a 10% incidence of spontaneous tears during routine follow-up examinations in at risk patients. These typically occurred in eyes with late fluorescent pigment epithelial detachments, and usually within a few months of presentation.

To our knowledge the characterisation of scotomata associated with RPE tears has not been considered. For this reason the reproducible quantification of associated scotomata by computerised visual fields was performed to evaluate the visual field loss and compare it with the clinical and fluorescein angiographic appearance.

Patients and methods

Two patients aged 60 and 70, were examined on the Wills Eye Retina Service for age related macular degeneration with associated pigment epithelial detachment. Both were noted to develop spontaneous tears of the retinal pigment epithelium. Neither patient had clinical evidence or a past history compatible with glaucoma, optic neuropathy, or retinal vascular disease.

Computerised visual fields were calculated by the Octopus 201 static perimeter. Basic software programs 31 and 32 were used to define grossly the visual field abnormalities. Higher resolution, with detailed definition of the defects, was obtained with advanced software. Octopus multiple-use user defined programs (UDP) CO-4 and CO-8 were employed. Both patients gave reliable responses to the tests.

Initial testing was carried out with standard 30° radius visual fields with 6° of resolution (programs 31 and 32). These programs were useful in attempting to roughly define the location, size, shape, and contour of the scotomas. Multiple-use UDP programs CO-4 and CO-8 were then used to define closely the visual field loss. Resolution of 1° and 2°, respectively, allowed detailed characterisation of the scotoma. CO-8 is an 8° radius visual field, CO-4 is a 4° radius visual field; both test 57 points, double determining nine of these points.

Case reports

CASE I

A 70-year-old male was first seen in September 1981 complaining of decreased vision and metamorphopsia in his left eye. His visual acuity was 20/25 in the right eye and 20/400 in the left eye. Funduscopic examination revealed changes consistent with bilateral age related macular degeneration (ARMD) and a subretinal neovascular membrane in the left macula.

Subsequent follow-up was uneventful until March of 1986, when a detachment of the retinal pigment epithelium was observed inferotemporal to the fovea in the right eye; visual acuity was 20/30. Six weeks later the patient noted a sudden decrease in vision to 20/80. A pigment epithelial tear, along the temporal edge of the previously recorded pigment epithelilal detachment (PED), was noted. Nasal retraction of the pigment epithelium exposed underlying choroid up to the edge of fixation.

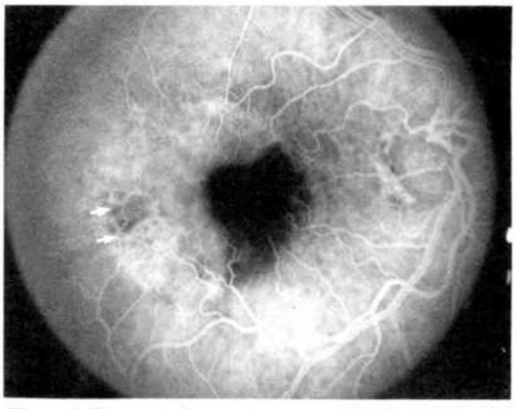


Figure 1: Case 1. A fluorescein angiogram at 36 seconds after injection shows early hyperfluorescence in the area of absent retinal pigment epithelium (arrows).

Retina Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, USA
J I Maguire
W H Annesley Jr
W L Decker
G C Brown
D H Fischer
J M Slagle

Correspondence to:
Joseph I Maguire, MD, Retina Service, Wills Eye Hospital, Ninth and Walnut Streets, Philadelphia, PA 19107, USA.

Accepted for publication
22 February 1990

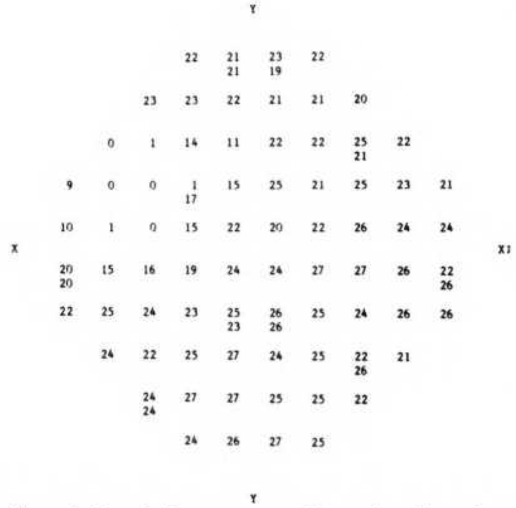


Figure 2: Case 1. Octopus program 32 grossly outlines a large area of marked decibel loss just superonasal to fixation in the right eye.

Fluorescein angiography showed a C-shaped area of mottled hyperfluorescence increasing in the late frames and corresponding to the exposed choroidal vasculature. The retracted pigment epithelium resulted in block choroidal fluroescence (Fig 1).

Octopus computerised static perimetry was performed three weeks after diagnosis of the pigment epithelial tear. A standard 30° radius central visual field (program 32) was initially used to outline grossly the extent of the scotoma located superotemporal to fixation (Fig 2). Closer definition of the nasal aspect of the tear, with its retracted pigment epithelium, was accomplished with the UDP CO-8 (Fig 3). Both fields revealed an absolute or near absolute scotoma in areas with absent pigment epithelium. However, decibel loss in the area containing retracted pigment epithelium was minor.

CASE 2

A 60 year-old woman with a history of ARMD was seen in May 1982 with a history for several months of decreased visual acuity and distortion of her vision in the right eye. Visual acuity was 20/40 in the right eye and 20/30 in the left eye.

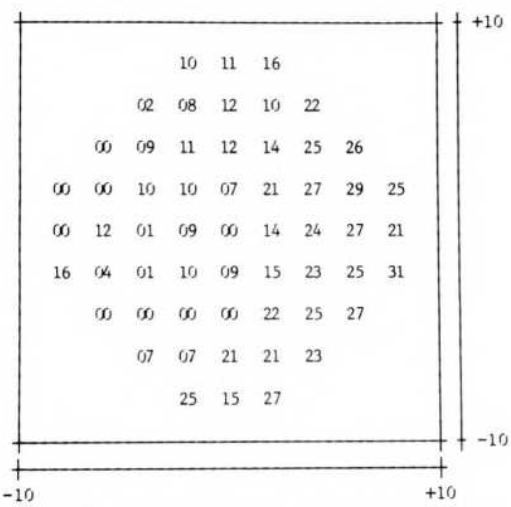


Figure 3: Case 1. Closer evaluation of the right eye with the CO-8 program details a dense central scotoma with a border of moderate decibel loss.

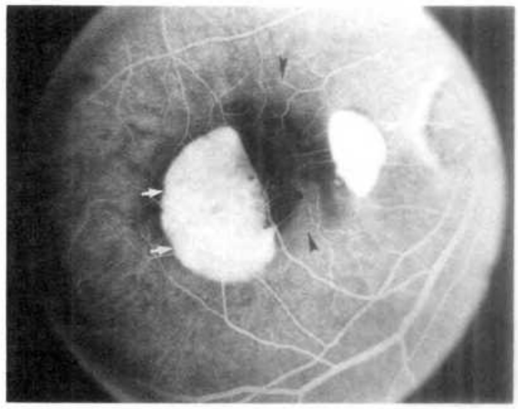


Figure 4: Case 2. Fluorescein angiography of the right eye at 35 seconds after injection discloses hyperfluorescence in the area of absent retinal pigment epithelium (arrows). The pigment epithelium has retracted centrally towards the fovea black (arrowheads).

Funduscopic examination revealed a PED of the left eye with scattered drusen. The right eye had numerous drusen and a double pigment epithelial tear. One tear was nasal and the other temporal to fixation. Fluorescein angiography showed retraction of the retinal pigment epithelium centrally on both sides of the fovea. Areas where retinal pigment epithelial was absent showed marked hyperfluorescence (Fig 4).

Octopus computerised static perimetry was performed one year later with a standard 30° radius field, which failed to delineate visual field loss (Fig 5). Higher resolution UDP programs CO-4 and CO-8, however, defined precisely the position of absolute decibel loss corresponding to the clinical position of the two pigment epithelial tears. Normal visual function was maintained centrally between the tears where retracted pigment epithelium was present (Fig 5, 6, 7). Sixty months after initial presentation the patient's clinical appearance and visual acuity remain unchanged.

Discussion

Tears of the retinal pigment epithelium are a known complication of pigment epithelial

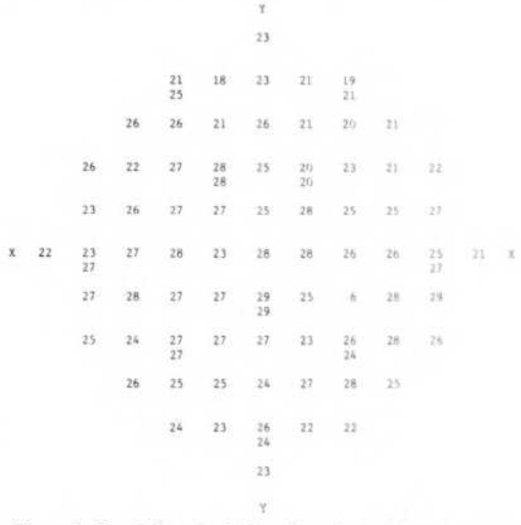


Figure 5: Case 2 Standard 30° radius visual field fails to show defects.

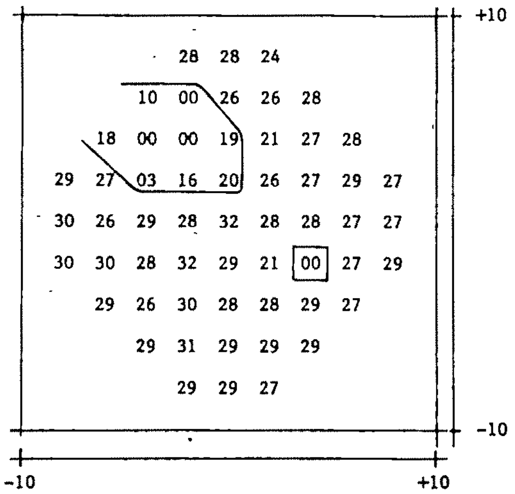


Figure 6

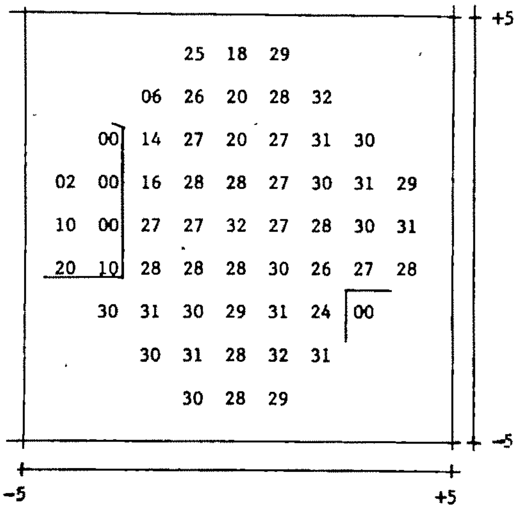


Figure 7

Figures 6 and 7: Case 2. CO-8 and CO-4 visual fields, respectively, are able to resolve two areas of absolute scotomata. These field defects correspond to the areas of absent retinal pigment epithelium. Fixation is preserved, which explains continued normal visual acuity.

detachments associated with ARMD. They result in retraction of the pigment epithelial layer towards the PED centre and away from the line of cleavage. The overlying sensory retina remains intact but unsupported by the retinal pigment epithelial monolayer. Angiographically, retracted retinal pigment epithelium blocks choroidal fluorescence, whereas adjacent areas devoid of retinal pigment epithelium are hyperfluorescent.

Although tears occurring in the central macular area have a poor visual prognosis, the nature and density of the resultant scotomas have not been well described. Computerised static perimetry, with resolution up to 1° of visual field, allows characterisation of the resultant scotomas when compared with the clinical appearance. In our two patients an absolute scotoma developed where retinal pigment epithelium no longer supported sensory retina. Conversely, adjacent areas containing retracted retinal pigment epithelium continued to function at normal or near normal levels, with minimal or no decibel loss. Although the patient described in our first case had visual field testing within one month after his retinal pigment epithelial tear, our second patient was not tested until one year afterwards. Both had absolute visual field defects implying the permanence of these changes.

The onset of visual dysfunction probably depends on loss of the physical, and therefore metabolic link between photoreceptors and pigment epithelium. Hoskin and colleagues' report noted one patient whose visual acuity decreased from 20/30 to 20/200 over several days after a tear developed.[1] This drop in vision coincided with the onset of structural changes described in animal models of sensory retinal detachments.[8] Of the 44 eyes with pigment epithelial tears reported by Hoskin and associates only eight retained a normal anatomical relationship between foveal retinal pigment epithelium and photoreceptors.[1] All, as in case 2, retained good visual acuity.

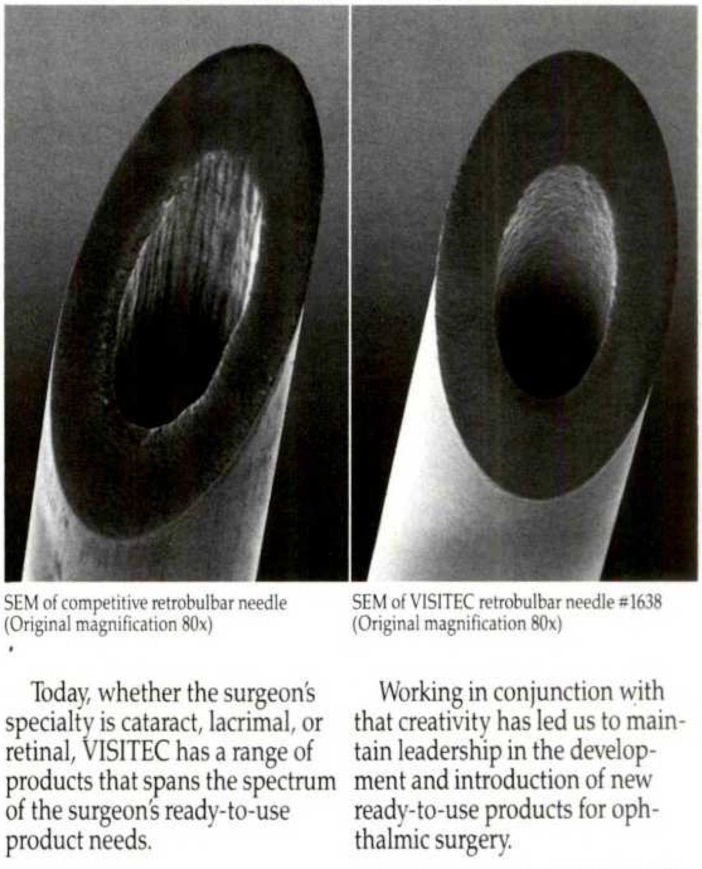
This work was supported in part by the Retina Research and Development Foundation, Philadephia

1 Hoskin A, Bird AC, Sehmi K. Tears of detached retinal pigment epithelium. *Br J Ophthalmol* 1981; 65: 417–22.
2 Gass JDM. Pathogenesis of tears of the retinal pigment epithelium. *Br J Ophthalmol* 1984; 68: 513–9.
3 Moorfields Macula Study Group Retinal pigment epithelial detachments in the elderly a controlled trial of argon laser photocoagulation. *Br J Ophthalmol* 1982; 66: 1–16
4 Elman MJ, Fine SL, Murphy RP, *et al.* The natural history of serous retinal pigment epithelium detachment in patients with age-related macular degeneration. *Ophthalmology* 1986, 93: 224–30.
5 Casswell AG, Kohen D, Bird AC. Retinal pigment epithelial detachments in the elderly: classification and outcome. *Br J Ophthalmol* 1985; 69: 397–403.
6 Decker WL Sanborn GE, Ridley M, *et al.* Retinal pigment epithelial tears *Ophthalmology* 1983; 90: 507–12.
7 Chaung EL, Bird AC. The pathogenesis of tears of the retinal pigment epithelium. *Am J Ophthalmol* 1988; 105: 285–90.
8 Kroll AJ, Machemer R. Experimental detachment in the owl monkey III Electron microscopy of the retina and pigment epithelium. *Am J Ophthalmol* 1968, 85: 410–27.

In ophthalmic surgery

READY TO USE FROM START TO FINISH

The superior finish quality of VISITEC products is evident



SEM of competitive retrobulbar needle (Original magnification 80x)

SEM of VISITEC retrobulbar needle #1638 (Original magnification 80x)

From pre-op through post-op

We've studied ophthalmic surgery from the time the patient enters pre-op through post-op care. The result is not only the most extensive ready-to-use product line, but more importantly, a line that simplifies each phase of ophthalmic surgery by extending all the benefits of ready-to-use to all involved in the surgical procedure.

... no matter what your surgical specialty

We've evolved alongside modern ophthalmic surgery and so has our line of ready-to-use products.

WORLD HEADQUARTERS
VISITEC Company
7575 Commerce Court
Sarasota, FL 34243
(800) 237-2174
(813) 351-9883
FAX: (813) 359-2015
TELEX: 5106000179

Today, whether the surgeon's specialty is cataract, lacrimal, or retinal, VISITEC has a range of products that spans the spectrum of the surgeon's ready-to-use product needs.

...we bring you the broadest and deepest ready-to-use product line

We recognize creativity as the driving force behind the evolution of technique.

Working in conjunction with that creativity has led us to maintain leadership in the development and introduction of new ready-to-use products for ophthalmic surgery.

One glance at our catalog will show that no company offers a broader range or more depth of selection than VISITEC.

With greater dedication to product quality and customer service

Unlike many others, we personally manufacture, inspect, and package every product that carries our name. The reason is simple – at VISITEC we stand behind the quality of our product 100%.

Likewise, our dedication to customer service begins with our sales and service representatives. Every one of them, on the phone or in the field, is professionally trained to provide prompt, courteous service, technical support and information to your entire team.

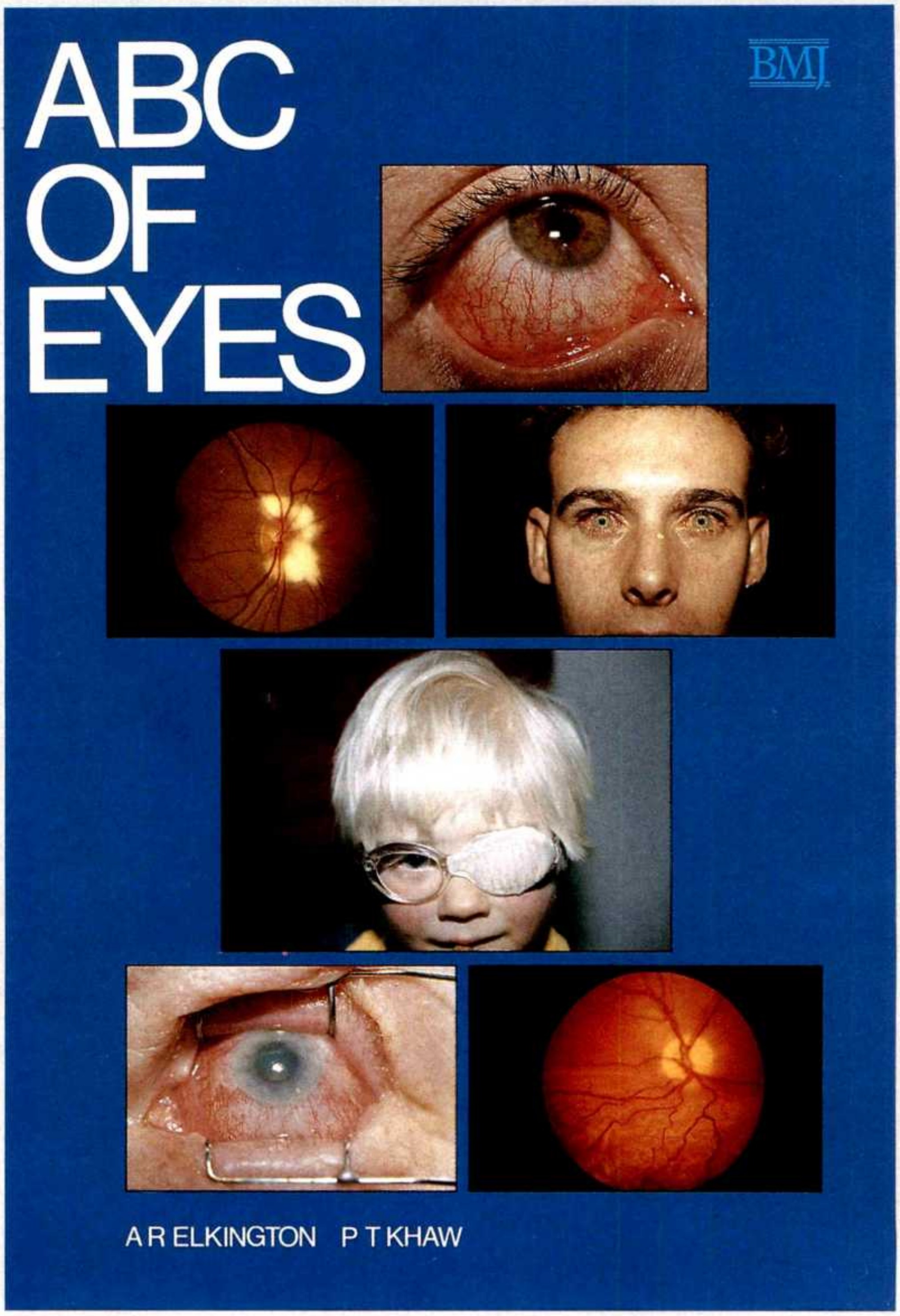
Product quality and customer service – we won't shift those responsibilities to anyone else.

Experience for yourself the superior quality only VISITEC ready-to-use products can offer. To place an order, or for a catalog, call toll-free: (800) 237-2174.

VISITEC®

QUALITY FOR ALL THE WORLD TO SEE

® Registered trademark of VISITEC Company. © Copyright 1989 VISITEC Company. All rights reserved.



Detailed descriptions of the symptoms and signs of common disorders of the eye together with **over 120 colour illustrations** make the *ABC of Eyes* an invaluable aid to diagnosis. Written by A R Elkington, senior lecturer and consultant ophthalmologist, University of Southampton, and P T Khaw, senior registrar in ophthalmology, Moorfields Eye Hospital, London, the book also provides guidance on when to refer to a specialist, and how urgently.

"... an excellent introduction to ophthalmology, for students and for the busy general physician ... presents basic ophthalmology with admirable simplicity, authority and clarity."
American Journal of Ophthalmology

"... students and family practitioners ... will find its short, relevant commentaries and sound clinical insights refreshing."
Canadian Medical Association Journal

Inland £10.95; Abroad £12.50
BMA members:
Inland £9.95; Abroad £11.50
including postage by air abroad

Please enclose payment with order
or send us full details of your
MASTERCARD, VISA or AMERICAN EXPRESS
credit card.

ORDER FROM British Medical Journal, PO Box 295, London WC1H 9TE or any leading bookseller

British Journal of Ophthalmology, 1990, 74, 559–560

MINI REVIEW

Management of intraocular melanoma

Prompt enucleation of the eye has been the conventional management of intraocular melanoma for at least 50 years. In spite of the radical nature of the surgery no follow-up study has shown any clear benefit in terms of improved patient survival. Indeed many studies have demonstrated an increased mortality during the first two years after enucleation – for example, the study of Benjamin *et al* reported in 1948.[1] Zimmerman and colleagues[2] were the first to suggest that enucleation might have an adverse effect on survival and claimed that dissemination of tumour cells during enucleation might predispose to subsequent metastatic death.

There is no doubt that the behaviour of intraocular melanoma is very variable, some tumours leading to early metastatic death while others behave in a relatively benign fashion. But even a prolonged tumour-free period after enucleation does not rule out the possibility of late metastatic death, for secondary tumours developing as long as 35 years after enucleation have been described.[3] It has been suggested that most intraocular melanomas shed malignant cells into the circulation from an early stage and probably when active growth is clinically detectable, and there is a consensus that in ways not at present understood the immune system may prevent the majority of such cells from developing into frank metastases.

Previously when the diagnosis of intraocular melanoma was made purely on clinical grounds mistakes were made in up to one-fifth of eyes enucleated.[4,5] Now that numerous ancillary investigations are available (fluorescein angiography, echography, CT scanning, magnetic resonance imaging, immunoscintigraphy, and surgical biopsy) mistakes are rare[6] and in centres specialising in ocular oncology occur in less than 1% of eyes removed for suspected melanoma. It is generally agreed that enucleation of an eye for melanoma should not be undertaken without a full diagnostic appraisal, and where doubt exists the patient should be seen in a centre experienced in the management of this tumour.

Zimmerman's suggestion that enucleation might have an adverse effect on survival in patients with melanoma has led to an increased interest in more conservative forms of management. The simplest form of conservative management is to keep the tumour under observation. Observation alone has, however, been followed by growth of the tumour in a significant proportion of cases,[7,8] and patients whose tumours grow may subsequently develop metastases (17% in one study[9]).

The major options for preserving the eye while eradicating the tumour lie between various forms of radiotherapy and local surgical resection of the tumour.

Melanoma is a radioresistant tumour requiring for its eradication a dose of radiation in excess of that which can be tolerated by many normal ocular tissues. To be used in the management of ocular melanoma radiotherapy has to be concentrated in the tumour and the dose to other radiosensitive ocular tissues minimised. Two main approaches have been used. Firstly the use of radioactive plaques containing such isotopes as ^{60}cobalt,[10] ^{125}iodine[11] (both of which are γ ray emitters), or ^{106}ruthenium/rhodium[12] (which is mainly a β ray emitter). An alternative treatment is by a beam of charged particles (protons or helium ions) accelerated in a cyclotron.[13,14] This procedure requires an expensive and sophisticated technology but can concentrate the radiotherapy within the tumour, with marked sparing of surrounding tissues, by making use of the physical characteristics of high energy particles. ^{60}Cobalt plaque therapy, first used by Stallard[10] in the management of intraocular melanoma, has been shown to be followed by a high incidence of late postirradiational vascular damage in the eye,[15] and none of the methods used for the radiotherapy of intraocular melanomas is entirely free from possible adverse irradiational side effects.

The other major form of treatment is local surgical resection, a method used for some 20 years in Glasgow[16] and now gaining acceptance in a number of other centres. The local resection of even sizeable tumours contiguous with the optic disc is possible, and indeed the results of treating posteriorly situated tumours by this technique are somewhat better than in the case of tumours involving both choroid and ciliary body.[17] The advantages of local resection in addition to the immediate elimination of the tumour are that histological confirmation is obtained, and information of prognostic significance is provided, such as the type of cells present in the tumour. The disadvantages are that immediate morbidity is higher than with radiotherapy, though interestingly the long term visual outcome may be better after successful local surgical resection than after radiotherapy, for a progressive loss of vision of the order of 10% per annum has been noted among eyes treated by radiotherapy.[18]

Although the preservation of vision is a commendable aim, the primary goal of treatment of uveal melanoma is the prevention of subsequent metastatic death. So far all the published statistics of radiotherapy or of surgical resection have shown no benefit of one method as against another or indeed of conservative management as against enucleation. Subsequent metastatic death appears to be determined mainly by whether or not there are epithelioid cells in the tumour and to less extent by such factors as the location of the tumour (anterior tumours having a poorer prognosis than posterior), the volume of the tumour, and the presence or absence of extrascleral spread. In relation to the last, some studies have shown by multivariate analysis that extrascleral spread is not a particularly important risk factor on its own, merely that it points to an adverse cell type in the tumour.[19]

At present we thus have at our disposal a number of methods for the control of the local disease. The choice of treatment is greater for smaller than larger tumours, all forms of management being suitable for tumours of up to 10 mm in diameter and up to 4 mm in thickness (laser photocoagulation, surgical resection, plaque therapy). For tumours in the range 10–15 mm in diameter local surgical resection, plaque therapy, or proton beam therapy may be indicated, while for larger tumours surgical resection or proton beam therapy may be employed, though enucleation is still required for very large tumours not susceptible to conservative management.

No treatment seems to be of value in improving survival, and the assumption has to be that most patients with an adverse cell type in the tumour already have micrometastases at the time of diagnosis. At present the goal of the ocular oncologist is to devise methods aimed at destroying subclinical micrometastases in the hope of improving survival, and secondly to improve techniques for the local control of the tumour to achieve the lowest morbidity and best visual acuity in both the short and the long term.

Although the evidence so far suggests that various forms of conservative management of uveal melanoma are comparable to enucleation in terms of subsequent survival, the absence of any really firm data has prompted the establishment of a co-operative multicentric trial in the United States to compare the results of local plaque delivered radiotherapy and enucleation in terms of survival.[20] Many aspects of this study have been criticised, but there is no doubt that useful information will eventually be obtained – though the cost at some $20 million is high.

Though excellent techniques are available to control the local disease, there is still some controversy about which size or location of tumour is best suited to one or other of the available methods of treatment. New techniques such as ultrasound or microwave induced hyperthermia in the tumour and photochemotherapy are being assessed, as is the use of chemotherapy, including the theoretical possibility of linking cytotoxic drugs or suitable radionucleotides to monoclonal antibodies against melanoma antigens in the hope of increasing the specificity of tumour destruction.

As matters stand at present, enucleation of the eye for melanoma is now regarded as an infrequent and 'last ditch' method of treatment.

WALLACE S FOULDS

Ross Hall Hospital,
221 Crookston Road,
Glasgow G52 3NQ

1 Benjamin B, Cummings JN, Goldsmith AJB, Sorsby A. Prognosis in uveal melanoma. *Br J Ophthalmol* 1948; 32: 729–47.
2 Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells? *Br J Ophthalmol* 1978, 62: 420–5.
3 Newton FH. Malignant melanoma of choroid. *Arch Ophthalmol* 1965; 73: 198.
4 Ferry AP. Lesions mistaken for malignant melanoma of the posterior area a clinicopathologic analysis of 100 cases with ophthalmoscopically visible lesions *Arch Ophthalmol* 1964; 72: 463–9
5 Zimmerman LE. Problems in the diagnosis of malignant melanomas of the choroid and ciliary body. *Am J Ophthalmol* 1973; 75: 917–29.
6 Blodi FC, Roy PE. The misdiagnosed choroidal melanoma. *Can J Ophthalmol* 1967; 2: 209–11.
7 Char DH, Hogan MG Management of small elevated pigmental choroidal lesions. *Br J Ophthalmol* 1977; 61: 54–8.
8 Gass JDM. Observation of suspected choroidal and ciliary body melanomas for evidence of growth prior to enucleation *Ophthalmology* 1980; 87: 523–8.
9 Gass JDM. Comparison of uveal melanoma growth rates with mitotic index and mortality *Arch Ophthalmol* 1985; 103: 924–31.
10 Stallard HB. Malignant melanoma of the choroid treated with radioactive applicators. *Trans Ophthalmol Soc UK* 1959; 79: 373–92.
11 Sealy R, le Roux PLM, Rapley F, Herring E, Shakelton D, Sevel D. The treatment of ophthalmic tumours with low energy sources *Br J Radiol* 1976; 49: 551–4
12 Lommatzsch PK. Experiences in the treatment of malignant melanoma of the choroid with ^{106}Ru-^{106}Rh beta-ray applicators. *Trans Ophthalmol Soc UK* 1973; 93: 119–32
13 Gragoudas ES, Goitein M, Verhey L, Munzenreider J, Suit HD, Koehler A. Proton beam irradiation an alternative to enucleation for intraocular melanomas. *Ophthalmology* 1980; 87: 571–81
14 Char DH, Saunders W, Castro JR, *et al.* Helium in therapy for choroidal melanoma *Ophthalmology* 1983, 90: 1219–25.
15 Macfaul PA, Bedford MA. Ocular complications after therapeutic irradiation *Br J Ophthalmol* 1970; 54: 237–47.
16 Foulds WS. Local excision of choroidal melanomas. *Trans Ophthalmol Soc UK* 1973, 93: 343–6.
17 Foulds WS, Damato BE, Burton RL. Local resection versus enucleation in the management of choroidal melanoma. *Eye* 1987; 1: 676–9.
18 Gragoudas ES, Seddong M, Egan K, *et al.* Long-term results of proton beam irradiated uveal melanomas. *Ophthalmology* 1987; 94: 349–53.
19 Kidd MN, Lyness RW, Paterson CC, Johnston PB, Archer DB. Prognostic factors in malignant melanoma of the choroid: a retrospective survey of cases occurring in Northern Ireland 1965–80 *Trans Ophthalmol Soc UK* 1986; 105: 114–21.
20 Schachat AP. Collaborative ocular melanoma study. In: Ryan SJ, ed. *Retina*. St Louis: Mosby, 1989; 1: 733–6.

British Journal of Ophthalmology, 1990, 74, 561–562

A case of fungal keratitis caused by *Scopulariopsis brevicaulis:* treatment with antifungal agents and penetrating keratoplasty

Nicola K Ragge, J C Dean Hart, D L Easty, A G Tyers

Abstract

A case of fungal keratitis caused by *Scopulariopsis brevicaulis* following a penetrating eye injury is described. Treatment with antifungal agents and keratoplasty resulted in a favourable outcome.

A 26-year-old scene shifter received a penetrating injury to the right eye from a rusty nail embedded in a rotting, wet, wooden plank. He immediately placed a soil covered hand up to his eye. He was admitted to hospital, where emergency suturing of a corneal perforation and extracapsular removal of an opacifying lens was performed. After improvement he was discharged on chloramphenicol 0·5% drops and prednisolone 0·5% drops, both four times a day. Two weeks later he was readmitted with a progressive keratitis of the right eye. Initial cultures were negative for bacteria, but the fungus *Scopulariopsis brevicaulis* was grown. Treatment with chloramphenicol 0·5% drops four times a day, prednisolone 0·5% drops once a day, and amphotericin B 0·5% drops hourly was instituted, with initial improvement. One week later a secondary uveitis developed, for which dexamethasone 0·1% drops two-hourly and cyclopentolate 1% drops three times a day were started in addition to pre-existing topical treatment. Two days later he presented at the Bristol Eye Hospital with increasing redness of the right eye and reduced visual acuity to hand movements; the left visual acuity was 6/5. A dense stromal infiltrate occupying two-thirds of the cornea and a 3–4 mm hypopyon were present in the right eye. The posterior capsule was intact. A red reflex was obtained but no fundal detail. The left eye was quiet. The patient was fit except for mild asthma, treated with salbutamol inhalers but never steroids. He was not diabetic. He had had recent episodes of 'thrush' in the groin area and 'athlete's foot', which had cleared. His white cell count and white cell function tests, especially responses to fungi, were normal. Antibodies to HIV (human immunotrophic virus) were not detected. No intraocular foreign body was seen on orbital radiography.

A corneal scrape revealed a few pus cells and later on culture yielded *Scopulariopsis brevicaulis*, confirming the previous report. An anterior chamber tap showed numerous pus cells but no organisms. Blood cultures were negative. The sensitivities of the organism were not available initially, but it was thought that treatment with amphotericin should be continued.

As endophthalmitis was suspected; amphotericin was instilled into the anterior chamber at the time of the tap at a dose of 1·25 μg in 0·1 ml. This was calculated as 1/4 of the accepted intravitreal dose.[1-3] Topical steroids were stopped and hourly amphotericin 0·5% drops and cyclopentolate 1% drops three times a day continued. In addition, intravenous amphotericin 0·25 mg/kg daily was given. After an initial improvement the hypopyon then increased and the cornea became more cloudy. On microbiological advice a new antifungal drug, itraconazole (Jansen Pharmaceuticals), was added at an initial dose of 200 mg twice a day orally for 24 hours, reducing to a maintenance dose of 100 mg twice a day. The clinical condition deteriorated further, and an emergency keratoplasty (8·5 mm donor button, with removal of an 8·0 mm disc of cornea, including all the involved cornea) was performed. Histological examination confirmed the mycotic keratitis with isolation of *Scopulariopsis brevicaulis*. Following keratoplasty dexamethasone 0·1% drops four times a day were given and the topical amphotericin 0·5% drops were reduced to four times daily. Intravenous amphotericin was stopped and oral itraconazole continued for three days.

The graft cleared and has remained transparent, with a visual acuity of 6/9 with a contact lens. Later the Mycological Reference Laboratory showed the organism was resistant to amphotericin B at 20 μg/ml but sensitive to itraconazole 2·0 μg/ml.

Discussion

Scopulariopsis brevicaulis is a saprophytic soil organism.[4] It has also been isolated from Californian beaches, caves in Mexico, and sauna baths in the German Democratic Republic.[5-7] It

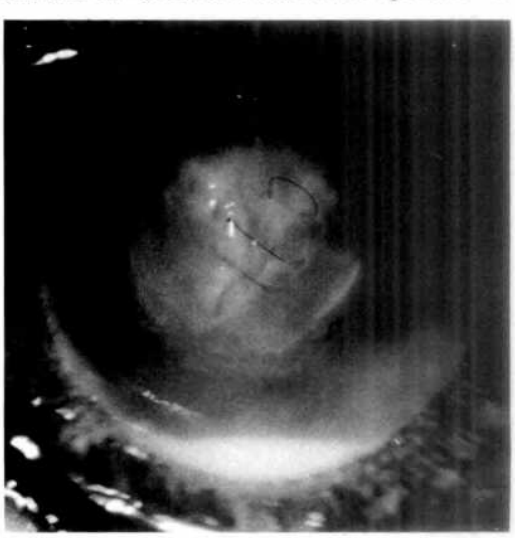


Figure 1: Fungal keratitis surrounding the sutured corneal wound in the case reported here.

Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX
N K Ragge
J C Dean Hart
D L Easty

Odstock Hospital, Salisbury
A G Tyers

Correspondence to:
Miss Nicola Ragge.

Accepted for publication 22 March 1990

is most frequently associated with nail infections in man,[8] though it has been isolated from tonsils and skin.[9 10] Sporadic cases of ocular infection have been recorded previously: one case of endophthalmitis following retinal detachment surgery when, despite therapy, the eye became phthisical and required enucleation;[11] one case of corneal ulcer with *Scopulariopsis* species in India, but with no further clinical details given;[12] and two cases of keratomycosis caused by *S. brevicaulis*, again with few details of the cases or outcome.[13] The infection in our case was probably acquired at the initial injury from soil contamination.

A variety of agents are effective against *S. brevicaulis* in vitro,[14] though the best one for treating *S. brevicaulis* infection in man is not at present known. Although antagonism between the sterols and imidazoles is often seen in vitro, combination therapy is used successfully in vivo.[15] Keratoplasty has been used successfully in the treatment of fungal keratitis in the past.[16 17]

The present case illustrates the importance of penetrating keratoplasty in removing the bulk of the fungal infection, allowing the antifungal therapy to act on any remaining infection. This should be performed immediately it is clear that medical therapy has failed to control the situation.

The authors acknowledge the help of Dr Sharon Patrick, consultant microbiologist, Odstock Hospital, Salisbury, and the Mycological Reference Laboratory, London, for initial identification of the organism, and Dr D Warnock, Department of Microbiology, Bristol Royal Infirmary, for subsequent confirmation and further advice. We are also grateful to Dr T Wallington, Department of Immunopathology, Southmead Hospital, for performing leucocyte function and immunological tests.

1 Forster RK. Endophthalmitis In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Harper and Row, 1987; 4: Chapter 24: 11.

2 Ho PC, Tolentino FI, Baker AS. Successful treatment of exogenous aspergillus endophthalmitis: a case report. *Br J Ophthalmol* 1984; 68: 412–5.

3 Perraut LE Jr, Perraut LE, Bleiman B, Lyons J Successful treatment of *Candida albicans* endophthalmitis with intravitreal amphotericin B. *Arch Ophthalmol* 1981; 99: 1565–7

4 Morton FJ, Smith G. The genera *Scopulariopsis* Bainer, *Microascus* Zukal, and *Doratomyces* Corda. *Mycological papers*. Commonwealth Mycological Institute, Kew, Surrey, United Kingdom, 1963: 86.

5 Dabrowa N, Landau JW, Newcomer VD, Plunkett OA. A survey of tide washed coastal areas of southern California for fungi potentially pathogenic to man. *Mycopathologia* 1964; 24: 137–50.

6 Gonzalez-Ochoa A, Dallal y Castillo E. Frecuencia de *Scopulariopsis brevicaulis* en muestras de suelos en cuevas y minas del pais (Incidence of *S. brevicaulis* in soil samples from caves and mines.) *Rev Inst Salubr Enferm Trop (Mex)* 1960; 20: 247–52.

7 Gemeinhardt H, Lange H Zur Vorkommen von Dermatophyten in Saunabadern. (The incidence of dermatophytes in sauna baths.) *Dermatol Monatsschr* 1974; 160: 268–77.

8 Walshe MM, English MP. Fungi in nails *Br J Dermatol* 1966; 78: 198–207.

9 Heymer T. Die Pilzflora der Tonsillen. (The fungal flora of the tonsils.) *Arch Klin Exp Dermatol* 1958; 208: 74–80.

10 Bazex A, Parant M, Ferrere J, Bazex J, Berger M. Infections à *Scopulariopsis brevicaulis*. Mise en évidence de son role pathogène. (*Scopulariopsis brevicaulis* infections. Evidence of its pathogenic role.) *Ann Dermatol Venereol* 1977, 104: 254–5.

11 Nitzulescu V, Niculescu M. Panophtalmie mycotique par *Scopulariopsis brevicaulis*. (Mycotic panophthalmitis caused by *Scopulariopsis brevicaulis*.) *Arch Roum Pathol Exp Microbiol* 1976; 35: 273–6.

12 Srivastava OP, Koul RL, Gupta SP. A survey of fungi from eye patients in Lucknow. *Indian J Ophthalmol* 1975; 24: 19–21

13 Fazakas S Zusammenfassender Bericht uber die sekundaren Mykosen bei Erkrankungen des Augenlikrandes, der Bindehaut und der Hornhaut. (Comprehensive report on the secondary mycoses in diseases of the margin of the eyelid, the conjunctiva, and the cornea.) *Ophthalmologica* 1959; 138: 108–18.

14 Sekhon AS Sensitivity of *Scopulariopsis brevicaulis* to some antimicrobial agents. *Mycopathologia* 1975; 57: 177–9.

15 Goodman DF, Stern WH Oral ketoconazole and intraocular amphotericin B for treatment of postoperative *Candida parapsilosis* endophthalmitis. *Arch Ophthalmol* 1987; 105: 172–3.

16 Savir H Anterior segment resection because of *Fusarium solani* keratitis and endophthalmitis *Arch Ophthalmol* 1984; 102: 824–5

17 Karimov MK, Malanova NL, Kossovskii LV. Lechebnaia Keratoplastika pri Mikozakh Rogovoi Bologchki. (Curative keratoplasty in mycosis of the cornea.) *Oftalmol Zh* 1980; 35: 484–6.

British Journal of Ophthalmology, 1990, 74, 563

Traumatic hyphaema in a haemophiliac

C D G Morsman, J Holmes

University Hospital of Wales, Cardiff
Department of Ophthalmology
C D G Morsman

Department of Haematology
J Holmes

Correspondence to:
Mr C D G Morsman,
Department of Ophthalmology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

Accepted for publication
22 March 1990

Abstract

A case is presented of a 9-year-old haemophiliac boy who sustained a traumatic hyphaema with secondary haemorrhage. Conservative management was successful in preventing complications, and normal vision was retained.

Traumatic and spontaneous hyphaema is uncommon in haemophiliacs.[1] Previous case reports[2,3] have highlighted the possible complications of corneal blood staining and glaucoma. Correct diagnosis and management is therefore important in the presence of a clotting disorder.

Case report

The patient is one of four brothers all affected with haemophilia A, his factor VIII level being 2%. He sustained a blow to his right eye when a tree branch sprang back at him. The eye was somewhat painful initially, though vision was subjectively normal. He was seen in the haematology department, where a subconjunctival haemorrhage was noted, and 460 units of factor VIII were given. The next day the situation seemed unchanged, and a further 690 units of factor VIII were given.

Three days after the initial injury the boy was woken by pain in his right eye and associated nausea. He also noticed reduction of vision. He was referred to the Ophthalmology Department, where vision was 6/36 owing to a 20% hyphaema. The intraocular pressure was normal.

Management was conservative, with five days bed rest and factor VIII (1150 units initially then 500 units twice daily). The hyphaema was absorbed spontaneously over three days; vision at that time being 6/4. Gonioscopy and funduscopy did not reveal any permanent ocular damage, though a slight iridoplegia was noted. No further problems were noted over the following month.

Discussion

It is probable that the patient had a small bleed, invisible to the naked eye, into the anterior chamber at the time of the original injury. Secondary bleeds usually occur during the following four days[4] and are presumably more likely in the presence of delayed clot stabilisation. The secondary bleed carries a higher risk of complications such as glaucoma, which can lead to optic nerve damage or corneal blood staining, which reduces vision and can take a year or more to clear.

Traumatic hyphaema is usually managed by bed rest, though some centres recommend systemic steroids or antifibrinolytic agents.[5] Clotting disorders require correction, and close observation is necessary to prevent the development of complications by means of ocular hypotensive agents, topical anti-inflammatory drugs, or surgical removal of the clot if necessary, particularly in the event of a secondary hyphaema.

We would recommend that cases of ocular trauma in patients with clotting disorders are discussed with an ophthalmologist even if no gross hyphaema is present. In haemophilia factor VIII should be given as soon as possible after the injury, and in the presence of even minor signs of intraocular haemorrhage, admission to hospital, with regular factor VIII infusions during the high risk period, should be considered.

We thank Professor A L Bloom and Mr J W Hunter for allowing us to report on their patient.

1 Rubenstein RA, Albert DM, Scheie HG Ocular complications of hemophilia *Arch Ophthalmol* 1966; 76: 230–2
2 Kobayashi H, Honda Y Intraocular haemorrhage in a patient with hemophilia. *Metab Ophthalmol* 1985, 5: 27–30
3 Lifshitz T, Yermiahu T, Biedner B, Yassur Y Traumatic total hyphema in a patient with severe hemophilia. *J Pediatr Ophthalmol Strabismus* 1986, 23· 80–1.
4 Eagling EM, Roper-Hall MJ. *Eye injuries* London: Butterworths, 1986; Chapter 5: 2–3.
5 Read JE, Crouch ER. Trauma: ruptures and bleeding. In. Duane TD, ed. *Clinical ophthalmology.* Philadelphia Harper and Row, 1985: 4: chapter 61 9

British Journal of Ophthalmology, 1990, 74, 564–565

Spontaneous reabsorption of a rubella cataract

George T H Smith, G Adrien Shun-Shin, Anthony J Bron

Clinical Cataract Research Unit, Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW.
G T H Smith
G A Shun-Shin
A J Bron

Correspondence to:
George T H Smith, FRCS, Clinical Cataract Research Unit, Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW.

Accepted for publication 10 April 1990

Abstract

A case of spontaneous reabsorption of a rubella cataract is presented. The morphology of the capsular bag is recorded by Scheimpflug slit image and retroillumination photography.

Rubella virus is a well established cause of congenital cataract,[1-4] the virus sometimes being cultured from the lens for as long as 30 months after birth.[2] Spontaneous reabsorption of cataract when the capsule is apparently intact is a rare event in humans.[4,5]

CASE REPORT

A baby boy presented in January 1974 aged 6 weeks when it was noticed that the right pupil was larger than the left.

On examination his left eye was microphthalmic and he had an immature cataract. The red reflex was present, though funduscopy was not possible. The right lens was clear, and funduscopy revealed a pigmentary retinopathy on that side. Surgery was not carried out, because lensectomy for a unilateral cataract was thought to carry a poor visual prognosis, especially in an eye that was microphthalmic.

His mother was believed to have had rubella at two weeks of gestation. The baby had a rubella titre of 1/512 in January 1974, but virus was not isolated from his tears.

Followed up at regular intervals in the clinic, he subsequently developed a rotary nystagmus and a left esotropia. Over the years it has been recorded that his left lens has become progressively thinner, and when he was reviewed in October 1988 the lens was described as being 'biscuit' shaped, with white flecks deposited inside the shrivelled capsular bag (Figs 1 and 2).

At his last attendance in October 1989 the anterior and posterior capsules were in apposition. The Scheimpflug photograph in Fig 3 shows the two leaves of the anterior and posterior capsule. The arrows point to intense scatter anterior and posterior to the opacities. Funduscopy was now possible, and a typical salt and pepper pigmentary retinopathy was observed.

The patient continues to manage well with a right visual acuity of 6/12. The vision in his left eye remains poor at counting fingers as a result of macular damage and dense amblyopia. He also suffers from sensorineural hearing loss and had a small ventricular septal defect diagnosed at birth.

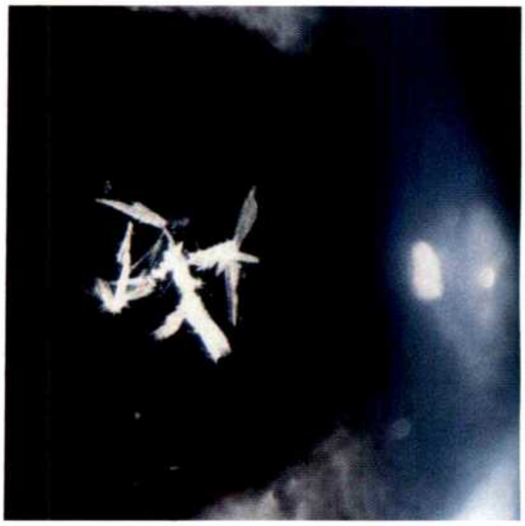


Figure 1: Colour photograph showing the white crystals which remained in the capsular bag after the cataract had been reabsorbed.

Discussion

Rubella cataracts occur in approximately 50% of cases of congenital rubella. The cataracts are bilateral in about 70% of cases and usually involve the nucleus, which is opaque.[2,3] The cataract may be associated with pigmentary retinopathy, microphthalmia, mesodermal dysgenesis, glaucoma, strabismus, and nystagmus.[3]

Possible spontaneous reabsorption of rubella cataract has been reported.[1,6-8] Ehrlich[1] reported a bilateral case in 1948 and described how on needling the remaining membrane no cortical matter was found and a clear pupil was achieved. His case was well documented, and he describes how the cataracts developed from being immature on presentation to becoming mature and then subsequently reabsorbing.

Gamble,[6] Blake,[7] and Long and Davidson[8] also describe their cases as being membranous but do not describe any progression from immaturity through maturity to becoming membranous. Blake suggested that his case might have been as a result of failure of lens fibres to develop rather than reabsorption.

The cause of spontaneous reabsorption of

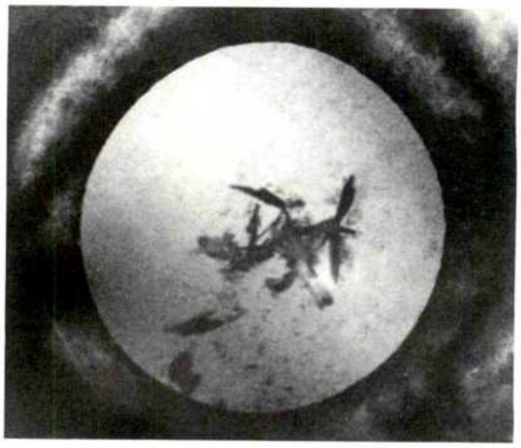


Figure 2: Retroillumination photograph showing the crystals silhouetted against the red reflex.

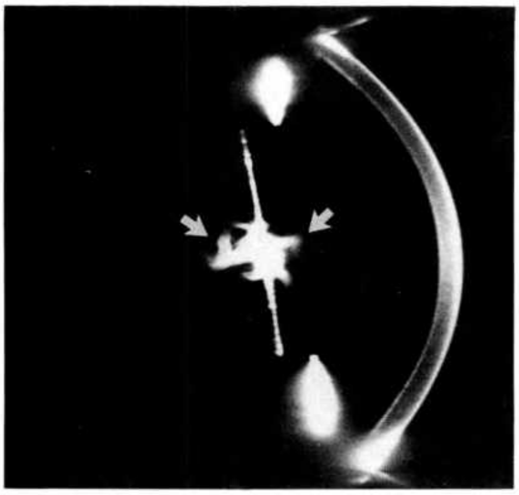


Figure 3: Scheimpflug photograph demonstrating the capsular bag. The arrows point to areas of intense scatter anterior and posterior to the white opacities.

cataract is unknown. It is well known that reabsorption can occur after rupture of the capsule,[4] but it is much more difficult to understand the mechanism in cases where the capsule remains intact. Possibly endogenous proteinase activity is responsible for the breakdown of the lens proteins, which can then leak out of an intact capsule.[9,10] Total reabsorption of a cataract is much more likely to occur in children than in adults, as the nucleus is more readily digested in immature lenses.[10]

The nature of the white crystals that remain within the capsular bag is uncertain, but they probably contain calcium oxalate as a result of dystrophic calcification.[5,10]

Scheimpflug and retroillumination photography are well recognised techniques for looking at the human lens in vivo.[11-14] In this case they clearly demonstrate the end result of spontaneous reabsorption of a congenital cataract due to rubella.

1 Ehrlich LH. Spontaneous absorption of congenital cataract following maternal rubella. *Arch Ophthalmol* 1948; **39:** 205–9.

2 Bellows JG. *Cataract and abnormalities of the lens*. New York: Grune and Stratton, 1975: 206–13.

3 Duane TD. *Clinical ophthalmology*. Philadelphia: Harper and Row, 1987; **5:** chapter 41:4.

4 Duke-Elder S. *System of ophthalmology*. X1, Diseases of the lens and vitreous. London: Kimpton, 1969; **11:** 138, 220–3.

5 Zimmerman LE, Hogan MJ. *Ophthalmic pathology, an atlas and textbook*. 2nd ed. Philadelphia: Saunders, 1962: 668–9.

6 Gamble RC. Membranous cataract due to rubella in the mother. *Am J Ophthalmol* 1946; **29:** 737–8.

7 Blake EM. Congenital membranous cataract. *Am J Ophthalmol* 1946; **29:** 464.

8 Long JL, Davidson RU. Cataracts and other congenital defects in infants following rubella in the mother. *Arch Ophthalmol* 1945; **34:** 24–7.

9 Trayhurn P, Van Heyningen R. Neutral proteinase activity in the human lens. *Exp Eye Res* 1976; **22:** 251–7.

10 Bron AJ, Habgood JO. Morgagnian cataract. *Trans Ophthalmol Soc UK* 1976; **96:** 265–76.

11 Brown NAP. Slit image photography. *Trans Ophthalmol Soc UK* 1969; **89:** 397–408.

12 Brown NAP. Quantitative slit image photography of the lens. *Trans Ophthalmol Soc UK* 1972; **92:** 303–17.

13 Brown NAP. The Oxford retro-illumination cataract recording camera – a new instrument. *J Audiov Media Med* 1988; **11:** 58–60.

14 Kawara T, Obazawa H. A new method for retro-illumination photography of cataractous lens opacities. *Am J Ophthalmol* 1980; **90:** 186–9.

British Journal of Ophthalmology, 1990, 74, 566–567

Progression of an iris melanoma over 41 years

David G Charteris

Princess Alexandra Eye Pavilion, Royal Infirmary of Edinburgh, Edinburgh EH3 9HA
D G Charteris

Correspondence to:
Mr D G Charteris,
Department of Pathology,
Institute of Ophthalmology,
17–25 Cayton Street, London
EC1V 9AT.

Accepted for publication
10 April 1990

Abstract

An iris melanoma first recorded in 1945 progressed over a period of 41 years to produce secondary glaucoma resulting in enucleation. The case illustrates the advancing nature of such lesions.

In 1945 a 37-year-old woman was noted to have a vascularised iris tumour inferonasal in her right eye (Fig 1). The lesion extended to the drainage angle, and a second small nodule was noted in the angle superonasally. Visual acuity was 6/6 in both eyes.

The lesion was observed, and a sectorial lens opacity developed after eight years. The tumour enlarged slowly. Between 1976 and 1986 there was recurrent haemorrhage into the anterior chamber, and secondary glaucoma developed (Figs 2, 3). Gonioscopy showed extension of the tumour round the drainage angle for 180°. Her visual acuity deteriorated to 6/60.

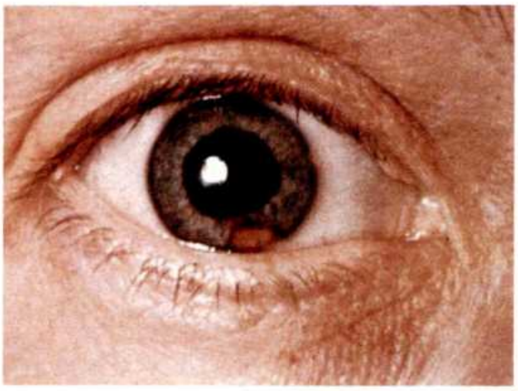


Figure 1: Appearance of the iris tumour in 1945. Note the small nodule peripherally between 2 and 3 o'clock.

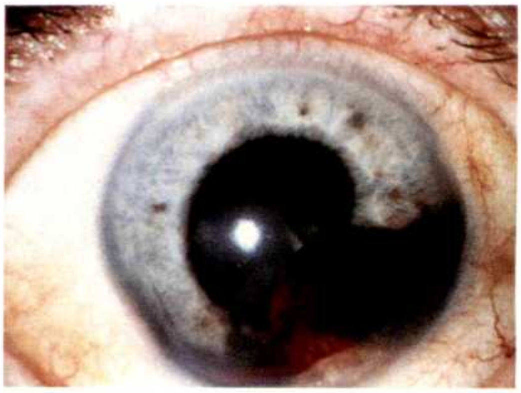


Figure 3: 1986 Recurrent haemorrhage and subsequent secondary glaucoma.

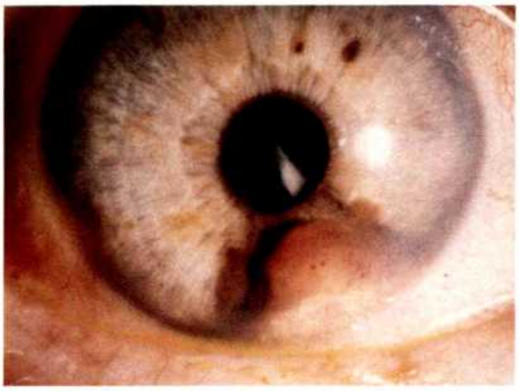


Figure 2: 1981 The tumour has enlarged and the lens is cataractous below.

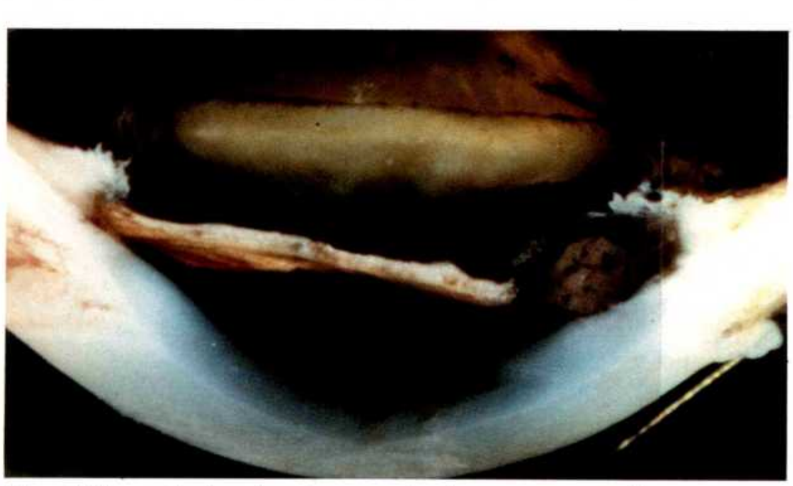


Figure 4: Macroscopic view of anterior segment showing tumour mass extending to drainage angle.

The eye was enucleated in 1986, and pathological examination revealed a lightly pigmented malignant melanoma of predominantly spindle B cell type. The tumour had extended to involve the drainage angle for almost 360° and showed some extension to the ciliary body (Figs 4–6). The patient has remained well since enucleation.

Discussion

The case emphasises the slowly progressive course of iris melanomas.[1-7] The lesion appeared fairly static for 30 years. It then spread round the angle to form a ring melanoma and was complicated by recurrent haemorrhage. Apparent lack of growth of iris melanocytic tumours may be due to very slow enlargement which can remain clinically undetectable over some years.[6] The slow progression of the tumour supports the current trend towards more conservative management of iris tumours,[4 6] the decision to enucleate being made because of intractable glaucoma. The change in behaviour may well reflect a change towards a more malignant cell type.[4 5] The case also provides an interesting early example of the use of colour photography to record clinical appearances.

The financial support of the Ross Foundation for Prevention of Blindness (Scotland) is gratefully acknowledged.

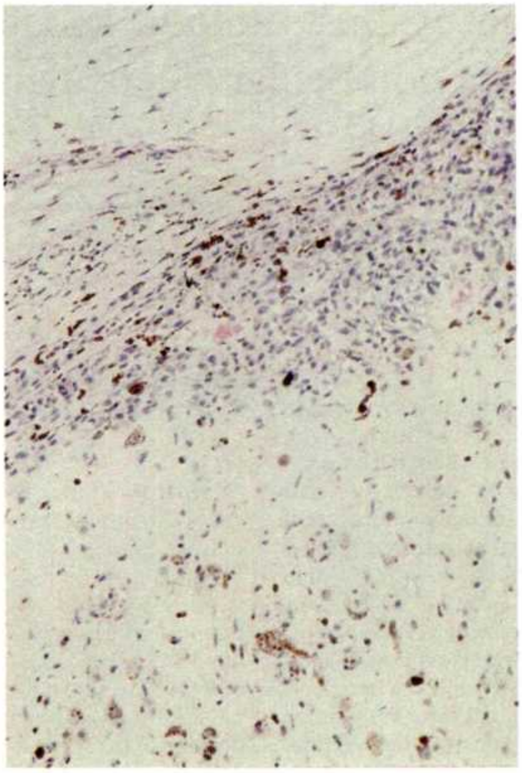


Figure 5: Photomicrograph showing lightly pigmented iris melanoma invading drainage angle structures. (H-E, ×100.)

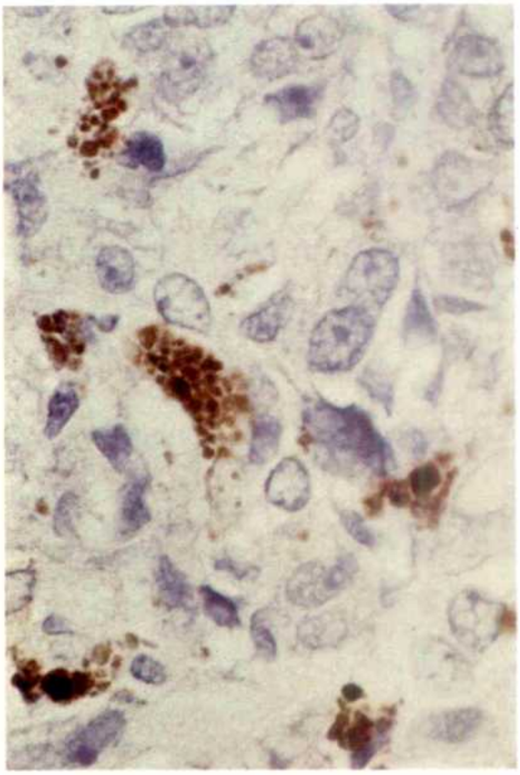


Figure 6: Higher power photomicrograph of spindle B iris malignant melanoma. (H-E, ×400.)

1 Duke JR, Dunn SN. Primary tumours of the iris. *Arch Ophthalmol* 1958; **59:** 204–14.

2 Rones B, Zimmerman LE. The prognosis of primary tumours of the iris treated by iridectomy. *Arch Ophthalmol* 1958; **60:** 193–205.

3 Ashton N. Primary tumours of the iris. *Br J Ophthalmol* 1964; **48:** 650–68.

4 Jakobiec FA, Silbert G. Are most iris 'melanomas' really nevi? *Arch Ophthalmol* 1981; **99:** 2117–32.

5 Geisse LJ, Robertson DM. Iris melanomas. *Am J Ophthalmol* 1985; **99:** 638–48.

6 Territo C, Shields CL, Shields JA, Augsburger JJ, Schroeder RP. Natural course of melanocytic tumours of the iris. *Ophthalmology* 1988; **95:** 1251–5.

7 McGalliard JN, Johnston PB. A study of iris melanoma in Northern Ireland. *Br J Ophthalmol* 1989; **73:** 591–5.

British Journal of Ophthalmology, 1990, 74, 568–570

11p13 Deletion, Wilms' tumour, and aniridia: unusual genetic, non-ocular and ocular features of three cases

Véronique Jotterand, Hélène M Boisjoly, Carmen Harnois, Pierre Bigonesse,
Rachel Laframboise, Richard Gagné, André St-Pierre

Centre Hospitalier de l'Université Laval, Québec, Canada
Department of Ophthalmology
V Jotterand
H M Boisjoly
C Harnois

Department of Paediatrics
P Bigonesse

Department of Genetics
R Laframboise
R Gagné

Department of Anaesthesiology
A St-Pierre

Correspondence to.
Dr H M Boisjoly, Unité de Recherche en Ophtalmologie, Université Laval, 2705 boul. Laurier, Québec, Canada
G1V 4G2

Accepted for publication
10 April 1990

Abstract

Three cases of Wilms' tumour and sporadic aniridia were followed up for periods ranging from 32 months to seven years. All had a deletion of the short arm of the eleventh chromosome 11p13, including one case with mosaicism, a cytogenetic feature that has not been previously described in the Wilms' tumour and sporadic aniridia association. Unusual non-ocular features found in all patients included tracheomalacia and delayed closure of the anterior fontanelle. In two cases tracheomalacia was responsible for respiratory distress after general anaesthesia. Wilms' tumour developed bilaterally in one patient and on the isthmus of a horseshoe kidney in another patient. In addition to the more commonly observed ocular features the presence of a corneal pannus was noted before 38 months of age in all patients and as early as 17 months in one case. An iridocorneal adherence with an overlying corneal opacity (presumably related to abnormal developmental cleavage of the anterior segment) was noted in one eye only of the mosaicism case.

Congenital aniridia can be sporadic or inherited as an autosomal dominant,[1 2] rarely as an autosomal recessive disease.[3] The majority of cases of aniridia with deletion 11p13 are sporadic. Approximately 68% of patients who have deletion of chromosome 11 and aniridia will develop Wilm's tumour before age 3 years.[4] There are now over 65 reported cases of the 11p13 depletion, Wilms' tumour, aniridia association.[4-9] In addition affected children often have genitourinary malformations, craniofacial dysmorphism, and developmental delay.[6] In this paper we summarise the genetic, non-ocular, and ocular manifestations and discuss the more unusual features found in three patients with 11p13 deletion, Wilms' tumour, aniridia association.

Features of the cases

The genetic, non-ocular, and ocular features of three cases of 11p13 deletion, Wilms' tumour, and aniridia are summarised in Tables 1, 2, and 3. Two girls and one boy, with normal family and pregnancy histories, were referred during their first months of life for diagnosis and follow-up aniridia. The visual function of these children, assessed by electrophysiological testing, has previously been described.[10] Cases 1 and 2 were followed up for seven years and their latest corrected visual acuities are 6/30 and 6/60 respectively.

GENETIC FEATURES (TABLE 1)

All the mothers had previously given birth to normal children. High resolution chromosomal banding analyses were performed in circulating white blood cells obtained from all cases and their parents as well as in Wilms' tumour cells obtained from cases 1 and 3. The parental chromosomes were normal. The children's white blood cells and Wilms' tumour cells presented a deletion of the short arm of the 11th chromosome with an interstitial deletion 11p13. Unexpectedly, only eight of 16 metaphases (50%) studied in the tumour cells of case 3 had the 11p13 deletion (Fig 1). The study of 34 metaphases in her white blood cells also demonstrated mosaicism with 23 normal cells (68%) and 11 abnormal cells (32%).

NON-OCULAR FEATURES (TABLE 2)

Facial dysmorphism of cases 1 and 2 was noticeable and similar (Fig 2). In case 3 facial dysmorphism was milder, with short downward slanted palpebral fissures as the only striking feature. All parents noticed that their child presented an unusual inspiratory stridor, especially after feeding or when lying supine. Tracheomalacia was diagnosed by direct visualisation with a laryngoscope in our three cases, and caused respiratory distress following general anaesthesia in cases 1 and 3. Another unusual

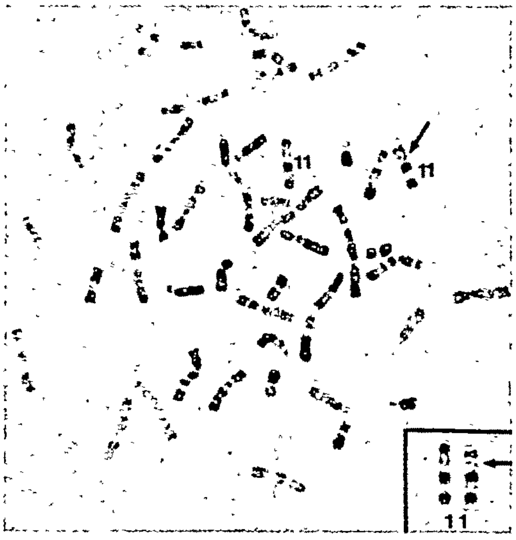


Figure 1 *Case 3. Mosaicism (46, xx/46, xx, del 11p13).*

Table 1 Genetic features

Case no.	Sibship	Mother's age (years) at birth	Cytogenetic studies: parents*	Cytogenetic studies: child*
1	2	27	Normal	del ll p 13
2	4	32	Normal	del 11 p 13
3	3	29	Normal	del ll p 3 mosaicism 50% normal leucocytes 68% normal Wilms' tumour cells

*The cytogenetic studies were done on circulating white blood cells of parents and children. Except for case 2, cytogenetic studies were also done on Wilms' tumour cells.

Table 2 Non-ocular features

Case no.	*Facial dysmorphism*	*Tracheomalacia*	*Age (months) at anterior fontanelle closure‡*	*Wilms' tumour location and age at diagnosis (months)*
1	Severe*	Present†	33	Unilateral, 29
2	Severe*	Present	26	Isthmus of horseshoe kidney, 10
3	Mild	Present†	24	Bilateral, 8

*The dysmorphic features included a long face, downward slanted palpebral fissures, a stubby nose, low set ears, a poorly demarcated long philtrum, and a thin superior lip. †These children suffered respiratory distress following anaesthesia. ‡The anterior fontanelle normally closes between 10 and 18 months of age.

*Table 3 Ocular features**

Case no.	*Age (months) at appearance of corneal pannus*	*Duration (months) of contact lens wear†*	*Location of polar cataracts*	*Unusual ocular features*
1	38	33	Anterior OU	None
2	32	3	Posterior OU	Tilted optic discs
3	17	Not fitted	Posterior OS	Iridocorneal adherence OS Localised absence of lens zonules OD

* All cases had foveal hypoplasia and normal intraocular pressures. †Contact lenses with artificial pupils worn during daytime.

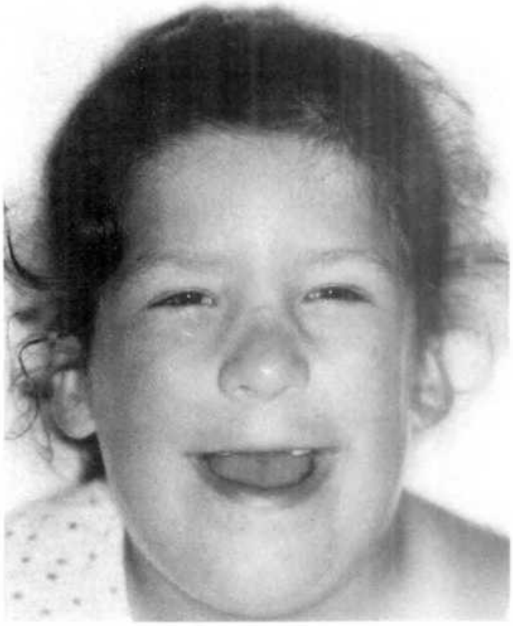


Figure 2 Case 1. Typical facial dysmorphism with a long face, downward slanted palpebral fissures, a stubby nose, low set ears, a poorly demarcated long philtrum, and a thin superior lip.

finding in these children was a delayed closure of the anterior fontanelle (the anterior fontanelle normally closes between 10 and 18 months of age). It was not accompanied by an abnormal electroencephalogram or skull *x*-ray, nor by abnormal blood calcium, phosphorus, alkaline phosphatase, and thyroxine levels. The fronto-occipital circumference was in the 50th percentile for cases 2 and 3 and in the 2nd percentile for case 1.

The location of Wilms' tumour was unusual in case 2. At age 10 months the child was admitted for haematuria and an abdominal mass. The abdominal ultrasound was difficult to interpret. A laparotomy with renal biopsy was performed and a stage II Wilms' tumour was found at the isthmus of a horseshoe kidney. The patient responded to a partial nephrectomy (isthmectomy) and chemotherapy. The outcome of case 3 with bilateral Wilms' tumours was poor. At 8 months of age an abdominal ultrasound showed a first mass measuring 4·0 cm in diameter located at the upper pole of the left kidney. An abdominal contrast-enhanced computed tomography revealed a second mass measuring 1·5 cm in diameter that ultrasound had failed to locate, seen at the hilum of the right kidney. Bilateral partial nephrectomies were performed. Well differentiated Wilms' tumours with no involvement of the regional nodes were found. A chemotherapeutic regimen combining actinomycin D and vincristine was started, but it was discontinued after four months because of renal failure and a generalised urticarial rash following vincristine treatment. The left kidney was found to be non-functional on intravenous urography at the age of 22 months. A recurrent tumour was found in the right kidney at the age of 25 months, and the child died at 32 months of age.

OCULAR FEATURES (TABLE 3)

All the children had foveal hypoplasia, polar cataracts (exceptionally, the cataract was unilateral in case 3), and normal intraocular pressures. Only case 1 wore contact lenses with artificial pupils during daytime on a regular basis for a significant amount of time. At age 38 months a peripheral inferior corneal pannus was noted for the first time, measuring 1·5 mm in width and progressing to 2·0 mm during the following two years. In case 2 a 1·0 mm peripheral inferior corneal pannus was noted at age 32 months. By age 41 months the pannus measured 2·0 mm wide in the left eye and 1·5 mm in the right eye. Tilted optic discs were also observed in this child. In case 3 a peripheral inferior corneal pannus measuring 1·0 mm wide was noted in both eyes at age 17 months. In addition an iridocorneal adherence, emerging from the rudimentary rim of the iris, with a paracentral corneal opacity overlying this adherence was found in the left eye only. Contralaterally the lens zonules were absent at the 10 o'clock position.

Discussion

We have described unusual genetic, non-ocular and ocular features in three cases of the 11p13 deletion, Wilms' tumour and aniridia association. The parents did not present genetic abnormalities. This is in accordance with the observation that in only three out of 15 reported families with a child having sporadic aniridia was one or other parent found to be a carrier of a chromosomal rearrangement.[11] Shannon and colleagues[12] reported a mean maternal age of 30·5 years (range 25–41 years) in the cases they reviewed and proposed that advanced maternal age might predispose to sporadic aniridia. In our case the mothers were not so old.

Our three cases support the fact that an 11p13 deletion associated with aniridia indicates a very high risk of development of Wilms' tumour. The genetic counselling to be offered to parents having a child with deletion mosaicism should probably be similar to that of other cases of 11p13 deletions.

In a review of aniridia up to 36% of patients with Wilms' tumour and aniridia had bilateral tumours.[13] Case 3 was found to have bilateral Wilms' tumours at the time of diagnosis. The smaller of the two tumours was not found on routine ultrasound but was detected only by contrast enhanced computed tomography. This stresses the importance of adding computed tomography to ultrasound for early detection of Wilms' tumour in these patients. Case 2 had a tumour on the isthmus of a horseshoe kidney. A case of a Wilms' tumour on a horseshoe kidney has also been described by Shannon *et al.*[12]

Tracheomalacia and delayed closure of the anterior fontanelle were found in all our cases. The clinical significance of a delayed fontanelle closure is not clear. Tracheomalacia, an insufficient cartilagious support of the trachea, can cause stridor or respiratory distress by tracheal collapse during periods of breathing efforts such as crying or exercising.[14] The diagnosis of tracheomalacia is made by endoscopic examination, when a tracheal collapse of 50% or more is observed.[15] The association of tracheomalacia and gastro-oesophageal reflux has been reported.[16] We observed that tracheomalacia caused respiratory distress after general anaesthesia during infancy in cases 1 and 3. Recently, at age 7 years, case 1 received an anaesthetic for an oesophageal foreign body obstruction; inspiratory stridor was again observed in the immediate postoperative period. Anaesthetists should therefore be informed of this possibility when children with aniridia are put under general anaesthesia.

The description of these cases adds new information on the time of appearance of corneal pannus in sporadic aniridia. Our observations suggest that it can appear as early as 17 months of age. Corneal pannus, also frequently recognised in adult autosomal dominant aniridia,[17] has been found in two adolescents with Wilms' tumour and aniridia, aged 13 and 14 years respectively.[18,19] The possibility that the pannus was related to contact lens wear is unlikely. The child (case 1) that wore contact lenses on a regular basis for almost three years developed a corneal pannus at a later age than the others.

We observed two unusual ocular features in case 3 that have not been previously described. An iridocorneal adherence was found in the left eye which is presumably related to abnormal developmental cleavage of the anterior segment. Even in autosomal aniridia, where iris anomalies can be variable, no such iridocorneal adherence has been described.[2,6] Secondly, a localised absence of lens zonules was found contralaterally. No coloboma of the iris, ciliary body, or choroid accompanied this lens zonule anomaly. It is not clear whether these one-sided ocular anomalies could be a manifestation of the 11p13 mosaicism observed in case 3.

In conclusion, sporadic aniridia should immediately alert ophthalmologists and paediatricians to the presence of other ocular and systemic anomalies and a strong possibility of a chromosomal abnormality, specifically the deletion of band 13 of the short arm of the 11th chromosome. Prompt assessment by a high resolution karyotype should be done with any child presenting with isolated aniridia. The presence of an 11p13 deletion indicates a very high risk of the development of a Wilms' tumour. Every patient with this deletion should be followed by a paediatrician, geneticist, oncologist, and ophthalmologist. Care should be taken to document all other congenital abnormalities, including trachemalacia, a previously unreported feature that can be responsible for respiratory distress after general anaesthesia.

1 Ferrell RE, Chakravarti A, Hittner HM, Riccardi VM. Autosomal dominant aniridia; Probable linkage to acid phosphatase-1 locus on chromosome 2 *Proc Natl Acad Sci* 1980; 77: 1580–2

2 Hittner HM, Riccardi VM, Ferrell RE, Borda RR, Justice J. Variable expressivity in autosomal dominant aniridia by clinical, electrophysiologic, and angiographic criteria. *Am J Ophthalmol* 1980; 89: 531–9

3 Gillespie FD. Aniridia, cerebellar ataxia and oligophrenia. *Arch Ophthalmol* 1965; 73: 338–41.

4 Turleau C, De Grouchy J, Tournade M-F, Gagnadoux M-F, Junien C. Del 11p/aniridia complex. Report of three patients and review of 37 observations from the literature. *Clinical Genetics* 1984; 26: 356–2

5 Smith AMC, Sujansky E, Riccardi VM. Aniridia, mental retardation and genital abnormality in two patients with 46xy 11p- *Birth Defects* 1977; 13: 257–265

6 Nelson LB, Spaeth GL, Nowinski TS, Margo CE, Jackson L. Aniridia. A review *Surv Ophthalmol* 1984, 28: 621–42.

7 Narahara K, Kikkawa K, Kimura S, *et al.* Regional mapping of catalase and Wilms' tumor-aniridia, genitourinary abnormalities, and mental retardation triad loci to the chromosome segment 11p1305p1306. *Hum Genet* 1984; 66: 181–185.

8 Bateman JB, Sparkes MC, Sparkes RS. Aniridia: enzyme studies in an 11p chromosomal deletion *Invest Ophthalmol Vis Sci* 1984; 25: 612–6

9 Mochon MC, Blanc JF, Plauchu H, Philip T. WAGR syndrome, Wilms' tumor, aniridia, gonadoblastoma, mental retardation a review of 2 cases. *Pediatrie* 1987; 42: 249–52.

10 Harnois C, Boisjoly HM, Jotterand V. Sporadic aniridia and Wilms' tumor. visual function evaluation of three cases. *Graef Arch Clin Exp* 1989; 227: 244–7.

11 Yunis JJ, Ramsay NKC. Familial occurrence of aniridia-Wilms' tumor syndrome with deletion 11p13–14 *J Pediatr* 1980; 96: 1027–30.

12 Shannon RS, Mann JR, Harper E, Harnden DG, Morten JEN, Herbert A. Wilms' tumor and aniridia: clinical and cytogenetic features *Arch Dis Child* 1982; 57: 685–90.

13 Knudson AG, Strong LC Mutation and cancer. A model for Wilms' tumor of the kidney. *J Natl Cancer Inst* 1972, 48: 313–24.

14 Wittenborg MH, Gyepes MT, Crocker D. Tracheal dynamics in infants with respiratory distress, stridor and collapsing trachea *Radiology* 1967, 88: 653–62

15 Campbell AH. Definition and causes of the tracheo-bronchial collapse syndrome. *Br J Dis Chest* 1967; 61: 1.

16 Couvreur J, Grimfeld A, Tournier G, *et al.* La dyskinésie trachéale (trachéomalacie) chez l'enfant. *Sem Hop Paris* 1981; 8: 688–97.

17 Mackman G, Brightbill FS, Optiz JM. Corneal changes in aniridia. *Am J Ophthalmol* 1979, 87: 497–502

18 Flaherty MP, Bousfield L, Sillence DO Aniridia resulting from chromosome 11p13 deletion (Miller's syndrome) report of a case. *Australian J Ophthalmol* 1984; 12: 197–202.

19 Kaiser-Kupfer MI, White BJ, Papadopoulos N Aniridia and mental retardation with deletion of the short arm of chromosome 11 *Tr Am Ophth Soc* 1981; 79: 276–93.

British Journal of Ophthalmology, 1990, **74**, 571–573

Self-enucleation and psychosis

Nicholas P Jones

University Department of Ophthalmology, Manchester Royal Eye Hospital
N P Jones

Correspondence to:
Mr N P Jones, University Department of Ophthalmology, Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH.

Accepted for publication
10 April 1990

Abstract

Four cases of self-enucleation are reported. Self-induced ocular mutilation is uncommon. Self-enucleation is rare and is specifically associated with paranoid delusions, either as a result of a drug-related toxic psychosis or in the functional psychoses, especially schizophrenia. An association with solvent abuse is reported. Such patients use self enucleation as a form of parasuicide and may mutilate themselves in other ways. In the management of such patients close co-operation between ophthalmologist and psychiatrist is important, as further self injury, including suicide is common.

Self-inflicted ocular injury is uncommon. In its mild forms, such as chemically or mechanically induced conjunctivitis, it may be a manifestation of malingering[1-3] or neurosis.[4] The problem is occasionally encountered in children, where mental retardation is usually the underlying problem,[5 6] but congenital corneal anaesthesia may also be seen.[7] In adults more determined attempts at ocular damage[8-10] are usually associated with acute psychosis and rank with self-poisoning and other severe self-mutilation as forms of parasuicide. The most extreme ocular mutilation is self-enucleation. Four such cases are reported, and some consistent features are discussed.

Case reports

CASE 1

A man aged 24 years presented after having attempted enucleation of the left eye. On examination the eye could not perceive light and was proptosed and soft, with a total hyphaema (Fig 1). The conjunctiva was detached close to the limbus through 360° and was haemorrhagic. No scleral rupture was visible. The eye was capable of small movements in each cardinal position of gaze. The right eye was uninjured, had a visual acuity of 6/5, and gave a normal direct pupil reaction but no consensual reaction. There was no visual field defect on this side.

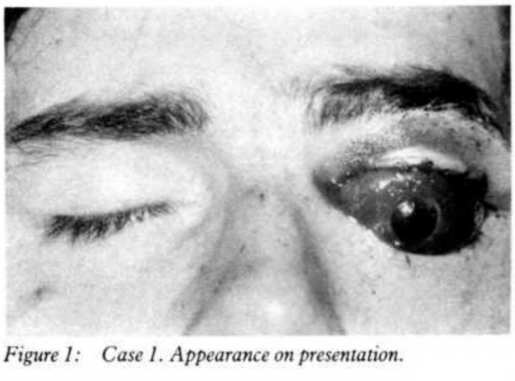


Figure 1: Case 1. Appearance on presentation.

The enucleation had been attempted by inserting his fifth finger through the lateral fornix and pulling forwards. He believed that 'I would not go to heaven unless I took it out', and 'I wanted to save my soul'. He said that 'the devil was after me' and he described both auditory and visual hallucinations which had instructed him to remove his eye. He abused amphetamines and marijuana regularly and lysergic acid diethylamide (LSD) occasionally.

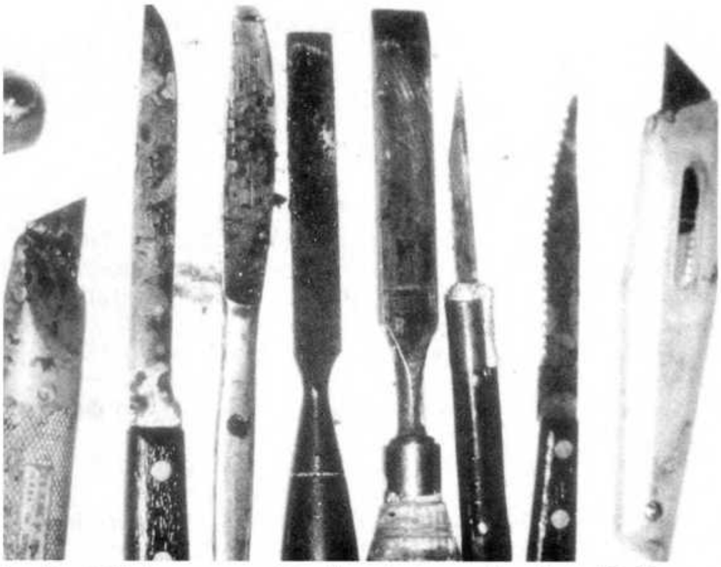
The patient was kept under constant nursing supervision because he had expressed suicidal tendencies. A diagnosis of drug induced psychosis was made and he was treated with thioridazine. The left globe and orbit were explored. A large scleral rupture was located superotemporally at the equator, with uveal prolapse. The rectus muscles were intact, but the optic nerve was completely avulsed. The eye was enucleated. An ocular prosthesis was fitted satisfactorily but two replacements were required because it was lost during subsequent psychotic episodes. His course was stormy and he committed suicide three years later.

CASE 2

A woman aged 43 years was found at home following attempted bilateral self-enucleation the previous day. She was a known schizophrenic but had not required medication for the preceding six months. She had a previous history of self-mutilation and had twice attempted to circumcise herself. She said, 'I have sinned against the Lord', and 'God told me to cut out my eyes' so 'I have punished myself' by doing so. In the almost completely successful attempt she had used a variety of sharp household instruments, including two wood chisels and kitchen and craft knives. This arsenal was brought to the hospital by an ambulance man, together with the left enucleated globe (Fig 2) in the hope that the latter was suitable for corneal donation. It was not.

On examination the right globe was present but could not perceive light. There was a full-thickness upper eyelid laceration, and the disrupted globe and orbital fat were prolapsed through the lids. The left globe was absent and the lids were closed by substantial eyelid haematomata (Fig 3).

The patient was admitted and treated with trifluoperazine. A CT scan demonstrated air in both orbits and in the prepontine and interpeduncular cisterns. Exploration of both orbits was performed under general anaesthesia. On the left side the conjunctiva was closed. On the right side there were extensive eyelid lacerations. The rectus muscles could not be located. Two full-thickness scleral lacerations were found inferotemporally, with vitreous loss and uveal prolapse. The anterior chamber was shallow and



2: *Case 2. The instruments used for self-enucleation, together with the left globe.*

contained substantial hyphaema. The pupil was fixed. The perforating injuries were repaired. Three days after surgery anterior segment necrosis supervened and the globe was enucleated.

The patient gained increasing insight within days, but some affective dissociation persisted. Ocular prostheses were fitted, with a good cosmetic result. No further attempts at self-mutilation have occurred.

CASE 3

A man aged 18 years perforated his left globe with a pencil and enucleated the eye with his fingers, completing the extraction with an ornamental kukri, which he then used to stab himself in the left hypochondrium. His father prevented him from sustaining more than a superficial laceration of the abdomen but entered the room after the enucleation had taken place. The patient was regularly taking amphetamine, cannabis, and LSD. He was also a frequent solvent abuser and on the night in question had been inhaling glue vapour. There was no previous history of self-mutilation.

On examination the left globe was absent. The right eye was undamaged and its visual field and pupil reaction were normal. After some persuasion the patient admitted that 'there was too much evil in the world' and that 'there are good eyes and evil eyes', so 'if I don't have the bad eye, I won't see any evil'. Parenteral penicillin and tetanus toxoid were administered, but the patient then refused any further parenteral treatment and would not contemplate surgery. Topical and oral antibiotics were administered. The attending psychiatrist thought that the self-mutilation had occurred as a result of delusions created by the use of drugs and solvent inhalation. Antipsychotic medication was not required. Satisfactory spontaneous healing of the orbit occurred and a prosthesis was successfully fitted. Insight into the effects of solvent abuse led to the cessation of this habit and there has been no further attempt at self-injury.

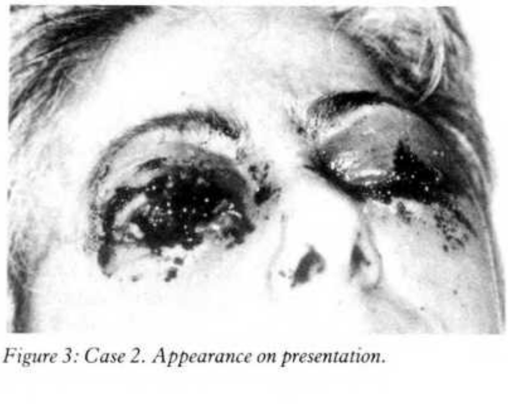


Figure 3: Case 2. Appearance on presentation.

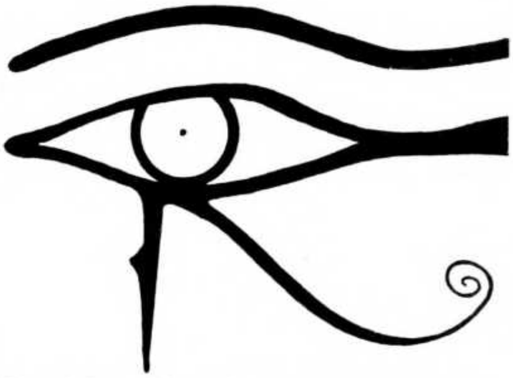


Figure 4: Case 4: The eye of Horus. A similar talisman was tattooed onto the left palm.

CASE 4

A 40-year-old man was committed to psychiatric care following a diagnosis of schizophrenia. He was a heroin addict, also abusing cannabis and cocaine. The palm of his left hand had been tattooed with the eye of Horus (Fig 4). He referred to this as his 'evil eye'.

On examination the right eye was absent. In a period of depression some months previously, during which he felt suicidal, he had removed the eye with his fingers, but had swallowed it as he 'didn't want to lose it'. Medical attention had not been sought, but he had given the socket regular lavage with saline. The socket was clean and the conjunctiva was well healed, allowing a reasonable inferior fornix. A prosthesis was fitted. No other self injury had occurred.

Three years after the self-enucleation of his first eye he attempted to remove his other eye with his fingers. He subluxed the globe but did not complete its removal. He voluntarily attended his psychiatric unit immediately, where the conjunctiva was noted to be chemosed and haemorrhagic, but there was no proptosis. The visual acuity was normal, as were the pupil reactions and visual field. There was no fundal abnormality. Some insight was expressed, but he could not give reasons for the attempted removal of his eye. He continues on depot pipothiazine in the management of his schizophrenia.

Discussion

Self-enucleation represents one end of a spectrum of severity in ocular self-injury.[11] But certain common features characterise the act of removal of the eye which are not seen in less severe forms of deliberate ocular damage. The condition is rare. The first documented case[12] occurred in 1836, and the term 'oedipism' was later suggested in deference to the Sophoclean character in the play *Oedipus Rex,* who had removed his own eyes in a state of guilt following the suicide of his mother. Other cases have been reported in the medical literature[13-19] and most have been reviewed by Krauss *et al.*[20] The term has occasionally been widened to include any form of ocular self-mutilation[8] but should properly be confined to self enucleation.

In previous reports of self-enucleation the almost constant association with functional and drug induced psychosis has been made.[9-11 14-20] Two of the above patients were schizophrenic, and three were abusing hallucinogenic drugs. One was probably suffering delusions induced by solvent inhalation at the time of self-enucleation. In cases of severe ocular self-injury the probability of drug involvement should be considered, and management modified accordingly.

The first two patients in this report described the need for expiation of guilt by the removal of an organ perceived as evil. The perception of an eye as intrinsically evil, or conveying evil images from an evil world, is a common thread in such instances, which is also exemplified in case 3. The avulsion of the offending organ does not necessarily produce the desired equanimity, and it is essential that such patients are closely supervised in an attempt to prevent further expressions of parasuicide, or suicide itself.[19]

Completed digital self-enucleation is remarkable in that it tends to cause little haemorrhage, conserves ample conjunctiva for the formation of a lower fornix, and is followed by uneventful healing, whether the conjunctiva is sutured or not. There have been no serious problems in the above cases in the fitting of prostheses. Blunt avulsion of the eye may involve a great length of optic nerve,[21] and the contralateral visual field may be at risk.[20]

Management of patients following self-enucleation must involve close co-operation between ophthalmologist and psychiatrist. Patients may not understand the implications of or may refuse treatment, and it may not be possible to insist on it. A psychiatrist considered that neither cases 1 nor 2 were fit to consent to surgery, and relatives consented on their behalf. A psychiatrist considered that in case 3 the underlying diagnosis of drug abuse, in the absence of an overtly psychotic state after admission, did not justify the use of Section 30(2) of the Mental Health Act 1959 to enforce treatment, even though the orbit had not been explored and repaired. Further self-injury is a real risk, as is shown by cases 1 and 4. Constant nursing supervision is necessary during inpatient ophthalmic treatment, and lengthy inpatient psychiatric care may subsequently be needed.

I am grateful to consultant ophthalmologists Mr C L Dodd, Mr E S Rosen, Mr J B Garston, and Mrs B Viswanathan, and to consultant psychiatrists Dr M F Osborne, Dr S Levine, and Dr A A Mallik, for their help in the preparation of this report, and to Mr A Prest for the preparation of illustrations

1 Somerset EJ Self-inflicted conjunctivitis *Br J Ophthalmol* 1945; **29:** 196–204
2 Somerville-Large LB Self-inflicted eye injuries *Trans Ophthalmol Soc UK* 1947; **67:** 185–201
3 Roper-Hall MJ Self-inflicted conjunctivitis *Br J Ophthalmol* 1950, **34:** 119–20
4 Jay JL, Grant S, Murray SB Keratoconjunctivitis artefacta *Br J Ophthalmol* 1982; **66:** 781–5
5 Noel L-P, Clarke WN Self-inflicted ocular injuries in children *Am J Ophthalmol* 1982, **94:** 630–3
6 Kinnas SJ, Brady HR. Oedipism and Down's syndrome case report and review of the literature. *Ann Ophthalmol* 1985, **17:** 431–3
7 Trope GE, Jay JL, Dudgeon J, Woodruff G Self-inflicted corneal injuries in children with congenital corneal anaesthesia. *Br J Ophthalmol* 1985; **69:** 551–4
8 Wilson WA. Oedipism *Am J Ophthalmol* 1955; **40:** 563–7
9 Yang KH, Brown GC, Magargal LE Self-inflicted ocular mutilation *Am J Ophthalmol* 1981; **91:** 658–63
10 Witherspoon CD, Feist FW, Morris RE, Feist RM *Ocular self-mutilation* *Ann Ophthalmol* 1989, **21:** 255–9
11 Duke-Elder S. Self-inflicted injuries In Duke-Elder S *System of ophthalmology* London Kimpton, 1966 14(1): 56–60.
12 Bergmann GH Ein Fall von religioses Monomanie, die eine unerharte Selbstvestummelung bei Geisteskranken *Z Augenheilkd* 1846; **1:** 128–51
13 Byrnes VA, Shier JM A case of self mutilation involving both eyes. *Am J Ophthalmol* 1949, **32:** 268–9
14 Rosen DH, Hoffman AM Focal suicide: self-enucleation by two young psychotic individuals *Am J Psychiatry* 1972, **128:** 1009–1012
15 Westermeyer J, Serposs A. A third case of self-enucleation *Am J Psychiatry* 1972, **129:** 144
16 Tamai M, Mizuno K, Okuyama S Self-inflicted proptosis misdiagnosed as orbital malignancy *Am J Ophthalmol* 1983; **96:** 812–4.
17 Jambur A, Kaplan HS, Keh-Ming L Self-inflicted enucleation of an eye two case reports. *Can J Psychiatry* 1984, **29:** 145–6
18 Stannard K, Leonard T, Holder G, Shilling J. Oedipism reviewed· a case of bilateral ocular self-mutilation *Br J Ophthalmol* 1984, **68:** 276–80
19 Khan JA, Buescher L, Ide CH, Pettigrove B Medical management of self-enucleation. *Arch Ophthalmol* 1985, **103:** 386–9
20 Krauss HR, Yee RD, Foos RY Autoenucleation *Surv Ophthalmol* 1984; **29:** 179–87.
21 Pillai S, Mahmood MA, Limaye SR. Complete avulsion of the globe and optic nerve. *Br J Ophthalmol* 1987, **71:** 69–72

British Journal of Ophthalmology, 1990, 74, 574–575

Lymphangioma circumscriptum of the eyelids and conjunctiva

R R Goble, M A Frangoulis

Abstract
A case of lymphangioma circumscriptum of the eyelids and conjunctiva is described. The classification of this disease is given.

The term 'lymphangioma circumscriptum' was introduced by Morris *et al* in 1889,[1] though the first case report had been described 20 years earlier.[2] It is an uncommon condition characterised by an area or areas of skin covered in clusters of persistent vesicles containing colourless fluid and sometimes blood. There may be associated subcutaneous thickening and cysts. It usually presents at birth or during early childhood, and the skin of the proximal limb and anterolateral trunk is most commonly involved.[3 4] We present a case with involvement of eyelid and conjunctiva.

Case report

A 19-year-old woman presented with a swollen right upper eyelid and numerous vesicles on the medial bulbar conjunctiva and eyelid margins. Some of the vesicles had bled following minor trauma. The lesions had first been noticed 10 years previously on the right caruncle and had been excised. They recurred two years after that operation, and more vesicles appeared on the adjacent conjunctiva and eyelids.

On examination the right medial canthus was covered in clusters of vesicles 1 mm in diameter. Most vesicles contained clear fluid, but several were blood filled (Fig 1). Both upper and lower eyelids were thickened medially, producing a mechanical ptosis of 2–3 mm. The lid lesions fluctuated in severity and were at worst only moderately noticeable. The conjunctival vesicles also varied in size, occasionally appearing pseudochemotic when confluent. No other skin lesions were found, and the ocular examination gave otherwise normal results, with no evidence of orbital involvement.

A clinical diagnosis of lymphangioma circumscriptum was supported by the previous biopsy report of lymphangiectasia. The eyelid margins were treated by cryotherapy with a liquid nitrogen spray to reduce the number of vesicles distorting the normal anatomy. It was felt that treatment to pretarsal tissue would fail to treat the deeper lesions adequately and would cause scarring. The conjunctival vesicles were the least noticeable and required no treatment.

Two months later there had been complete resolution of the blood filled marginal vesicles, with a minimal residual ptosis. Cosmesis was improved, and the patient refused any further treatment.

Sutton Eye Unit, Sutton Hospital, Cotswold Road, Sutton, Surrey SM2 5NF
R R Goble
M A Frangoulis

Correspondence to:
Miss M A Frangoulis.

Accepted for publication 19 April 1990

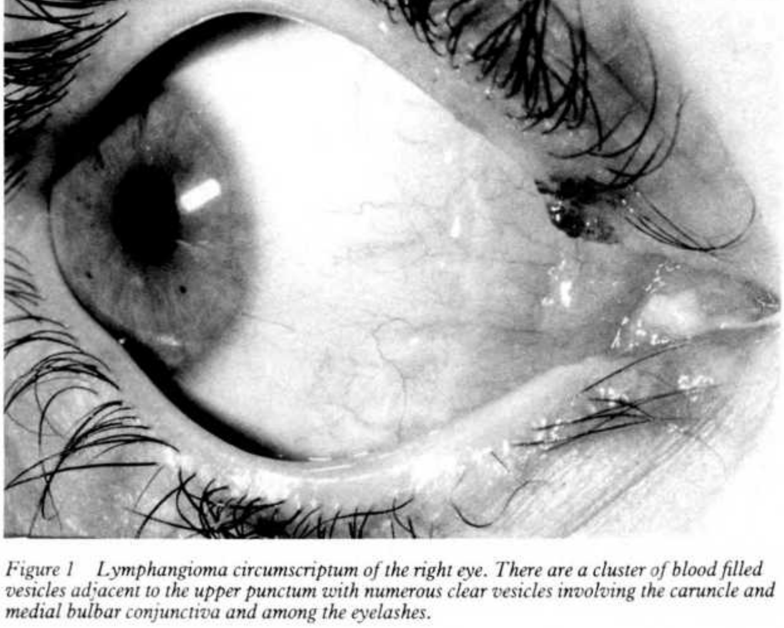


Figure 1 Lymphangioma circumscriptum of the right eye. There are a cluster of blood filled vesicles adjacent to the upper punctum with numerous clear vesicles involving the caruncle and medial bulbar conjunctiva and among the eyelashes.

Discussion

Lymphangioma circumscriptum is thought to represent a developmental abnormality. The subepidermal lymphatic 'vesicles' are endothelium-lined spaces which are completely separate from the normal lymphatic system.[5 6] Peachey *et al* described three groups of lymphangioma circumscriptum[6]:

(1) Classical lesions involving larger skin areas, which are produced by rhythmically contracting muscle coated cisterns in the subcutaneous tissues.[5] Other authors classify the subcutaneous lesions seperately as lymphangioma cavernosum.[4]

(2) Superficial lesions involving smaller areas with no subcutaneous abnormalities.

(3) Spongy lesions, found exclusively in areas where skin and mucosa are interwoven with striated muscle, such as tongue, lips, and eyelids. In the last group there are fewer vesicles and numerous irregular superficial dermal lymphatic spaces.

Treatment of superficial lymphangioma circumscriptum and the smaller classical lesions by surgical excision of skin and underlying subcutaneous tissue is 91–100% curative.[3 4] The larger classical lesions tend to recur following surgery, as the extent of subcutaneous involvement may be difficult to define, making complete excision impossible. Cautery, cryotherapy, radiotherapy, and carbon dioxide laser vaporisation have been used in treating surgically inaccessible sites, to improve cosmesis, and to prevent complications. However, none of these methods of treatment prevent recurrences in classical lesions.[6-9] It is difficult to evaluate different types of treatment in patients with lymphangioma circumscriptum because there have been no comparative trials.

1 Unna PG, Morris M, Duhring LA, Leloir H *International atlas of rare skin diseases*. London Lewis, 1889 1–4

2 Fox T, Fox TC On the case of lymphangiectodes with an account of the histology of the growth. *Trans Pathol Soc* 1879; 30: 470–6

3 Browse NL, Whimster IW, Stewart G, Helm CW, Wood JJ Surgical management of 'lymphangioma circumscriptum' *Br J Surg* 1986; 73: 585–8.

4 Flanagan BP, Helwig EB. Cutaneous lymphangioma. *Arch Dermatol* 1977; 113: 24–30.

5 Whimster IW. The pathology of lymphangioma circumscriptum. *Br J Derm* 1976, 94: 473–86

6 Peachey RDG, Lim C-C, Whimster IW. Lymphangioma of the skin. *Br J Derm* 1970; 83: 519–27

7 Van Cauwelaert P, Gruwez JA Experience with lymphangioma *Lymphology* 1978, 11: 43–8

8 O'Cathail S, Rostom AY, Johnson ML Successful control of lymphangioma circumscriptum by superficial *x*-rays

9 Eliezri ZD, Sklar JA Lymphangioma circumscriptum review and evaluation of carbon dioxide laser vapourisation *J Dermatol Surg Oncol* 1988; 14: 357–64

LETTERS TO THE EDITOR

Malignant glaucoma after laser iridectomy

Sir,—With reference to the article by Brooks, Harper, and Gillies,[1] we feel that the title 'Occurrence of malignant glaucoma after laser iridotomy' may be misleading. There are two reasons for the occurrence of malignant glaucoma in this case: the use of pilocarpine 4%, and the central retinal vein thrombosis. As the authors correctly pointed out in the discussion, pilocarpine and central retinal vein thrombosis are both recognised causes of malignant glaucoma. We therefore think that in this case malignant glaucoma was unrelated to the laser iridotomy.

O GEYER
L ROTHKOFF
M LAZAR
Ichilov Hospital,
6 Weizman Street,
Tel-Aviv 64239,
Israel

---

[1] Brooks AMV, Harper CA, Gillies WE. Occurrence of malignant melanoma after laser iridotomy *Br J Ophthalmol* 1989, **73:** 617–20

Sir,—We agree with Drs Geyer, Rothkoff, and Lazar that both the use of pilocarpine and the presence of central retinal vein thrombosis may be factors in the production of malignant glaucoma. However, in the patient we described the central retinal vein occlusion was noted on his presentation with typical acute angle closure glaucoma with a shallow but not flat anterior chamber, of the same measured depth as that of the fellow eye. The malignant glaucoma in this patient followed directly after the exhibition of pilocarpine 4% in the presence of a patent laser iridotomy and was accompanied by documented abrupt shallowing of the anterior chamber. This malignant glaucoma was relieved by mydriatic, particularly phenylephrine 10%. Even though some degree of angle closure recurred after discharge from hospital with the use of atropine but no phenylephrine the anterior chamber did not shallow, and the angle reopened when atropine was stopped, emphasising the instability of the lens-iris diaphragm in this patient.

Therefore, though in this patient malignant glaucoma followed immediately on the use of pilocarpine 4%, and the pre-existing central retinal vein occlusion may have been a contributory factor, it was not the precipitating factor. What appeared particularly important to us was that the presence of a patent iridotomy, performed by the non-invasive method of laser iridotomy, did not have a protective effect against the occurrence of malignant glaucoma. To our knowledge this has not previously been reported.

Since publishing our paper reports of two possible cases of malignant glaucoma following laser iridotomy have been drawn to our attention.[1,2] In one of these[1] it was concluded that the malignant glaucoma already existed prior to the laser. In the other[2] there was extensive laser iridoplasty as well as peripheral iridotomy, and a marked inflammatory element resulted. Neither of these cases clearly documents a case of malignant glaucoma following a simple patent laser iridotomy.

The title of our paper emphasises the important clinical finding that malignant glaucoma can be precipitated even in the presence of a patent laser iridotomy and we believe this title should stand.

ANNE M V BROOKS
C A HARPER
W E GILLIES
82 Collins Street,
Melbourne 3000,
Australia

---

[1] Takeuchi H, Okubo K. A case of malignant glaucoma occurring without past invasive surgery. *Jpn J Clin Ophthalmol* 1986; **40:** 399–402.

[2] Levene R. Malignant glaucoma: proposed definition and classification In: Shields MB, Pollack IP, Kolker AE, eds. Perspectives in glaucoma. *Transactions of first scientific meeting of the American Glaucoma Society* New Jersey Slack, 1988 243–50

NOTE

Ophthalmic echography

A course on standardised echography in ophthalmology will be held at the University Eye Hospital, Munich, West Germany, on 8–13 October, 1990. The English and German languages will be used in separate sessions. Further information from Professor Dr G Hassenfratz, Augenklinik der Universität Munchen, Mathildenstrasse 8, D-8000 Munchen 2, West Germany.

FIFTY YEARS AGO

Ophthalmic eye lithotrite for removal of non-magnetic intra-ocular foreign bodies

Dear Sirs,—Can any one tell me where I can obtain such an instrument?

Amongst my father's instruments, this is the one I valued most, and I found it invaluable for removing glass or other non-magnetic foreign bodies from the eye.

I understand it was made specially for him

Owing to being called up at short notice my own is in such a safe place I cannot find it. It consists of an ivory handle about three inches long containing a delicate spring controlled by a button lever, and the forceps portion extends to about one inch. The teeth open about an eighth of an inch when the spring is released To insert the forceps, which are very fine and delicate as no crushing is required, the teeth are closed by pressing the lever with the forefinger, then they are opened by releasing the lever and closed firmly on the foreign body to hold it and withdraw it.

In view of the large numbers of intra-ocular foreign bodies in wartime, and my colleague Mr L H. Savin tells me many are a compound of magnesium and aluminium, I thought this instrument would be of interest to your readers—also I want to replace my own.

Yours faithfully,
J. Myles Bickerton,
Wing-Comdr.

Br J Ophthalmol 1940, **24:** 414-5.

AJO
AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 00029394 August 1990 Series 3, Vol. 110, No. 2

TABLE OF CONTENTS

ORIGINAL ARTICLES

***Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy** Pravin U. Dugel, Narsing A. Rao, David J. Forster, Lawrence P. Chong, George T. Frangieh, and Fred Sattler

The natural course of central retinal vein occlusion Patricia M. Quinlan, Michael J. Elman, Amita Kaur Bhatt, Patrick Mardesich, and Cheryl Enger

Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity Michael F. Marmor, Samuel G. Jacobson, Michael H. Foerster, Ulrich Kellner, and Richard G. Weleber

Cellular immune responses of patients with uveitis to retinal antigens and their fragments Marc D de Smet, Joyce H. Yamamoto, Manabu Mochizuki, Igal Gery, Vijay K. Singh, Tochimichi Shinohara, Barbara Wiggert, Gerald J. Chader, and Robert B. Nussenblatt

Distinctive cataract in the Stickler syndrome Christopher M. Seery, Ronald C Pruett, Ruth M. Liberfarb, and Ben Z. Cohen

The results of penetrating keratoplasty for pelucid marginal corneal degeneration Gary A. Varley, Marian S. Macsai, and Jay H Krachmer

Enchondromatosis and hemangioma (Maffucci's syndrome) with orbital involvement Thomas E Johnson, Amin M Nasr, Robert M Nalbandian, and Ian Cappelen-Smith

Treatment of manifest latent nystagmus Alina A. Zubcov, Robert D. Reinecke, Irene Gottlob, Donelson R. Manley, and Joseph H. Calhoun

The fixed and dilated pupils of premature neonates Sherwin J. Isenberg, Althea Molarte, and Marisel Vazquez

An optical model to describe image contrast with bifocal intraocular lenses Neal H. Atebara and David Miller

Ab interno laser sclerostomy in aphakic patients with glaucoma and chronic inflammation Richard P. Wilson and Jonathan C. Javitt

Biometric variables in patients with occludable anterior chamber angles William C. Panek, Robert E Christensen, David A Lee, Doreen T. Fazio, Laura E Fox, and Timothy V Scott

A double-masked three-month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution Robert N. Weinreb, Delmar R. Caldwell, Stephen M. Goode, Barry L. Horwitz, Robert Laibovitz, C. Eric Shrader, Robert H. Stewart, and A Thomas Williams

Microbial contamination of contact lens storage cases and solutions Louis A. Wilson, Anil D. Sawant, Robert B. Simmons, and Donald G. Ahearn

Potential bacterial contamination in fluorescein-anesthetic solutions Lee R Duffner, Stephen C Pflugfelder, Sid Mandelbaum, and Linwood L Childress

LETTERS TO THE JOURNAL
CORRESPONDENCE
BOOK REVIEWS
ABSTRACTS
NEWS ITEMS

The AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. © 1990, Ophthalmic Publishing Company. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

MICHAEL J. LUND
Subscription Correspondent

LINDA G. CLAUSEN
Records Manager

LAUREEN A. KOTT
Assistant to the Editor

LYNN ANN LINDVIG
Sales and Production

KAREN D. JOHNSON
Manuscript Editor

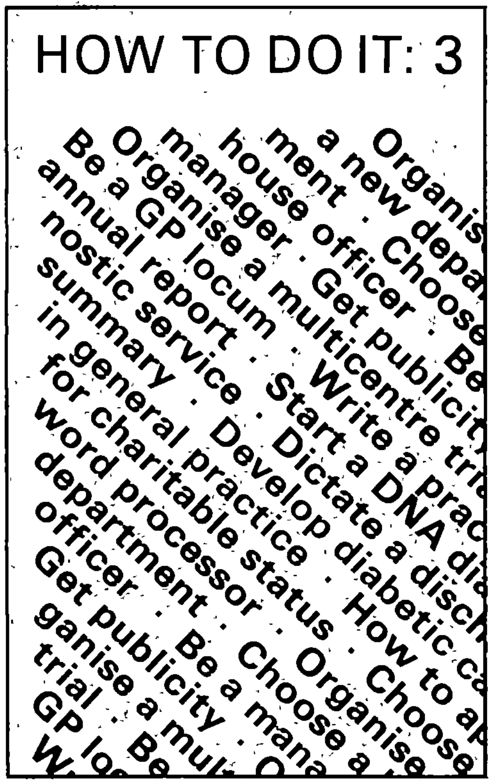
DIANN J. MARQUIS
Editorial Assistant

RENEE L. KASTAR
Assistant Media Planner

OPHTHALMIC PUBLISHING COMPANY

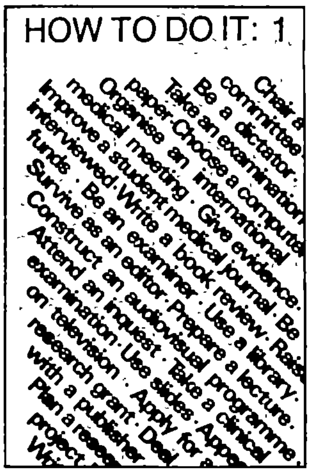
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611, U.S.A.

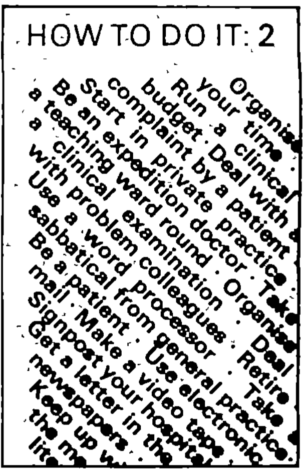
You don't know everything



But often in a medical career it seems as if you are expected to. When confronted with a problem you've never met before the only thing to do is to ask the experts—but where are the experts who are never on holiday, never off sick, in a meeting, or simply unavailable? In *How To Do It: 3*, that's where. You can keep them in your pocket, and in a few minutes they can tell you, among many other things, how to:

- lecture overseas
- be a manager
- prepare a Festschrift
- commission a portrait
- write a practice annual report
- organise multicentre trials
- start a DNA diagnostic service
- survive a dinner





Two companion volumes of essential know-how are also available

Price (each book): Inland £6.95; Abroad £9.00
BMA members: Inland £6.45; Abroad £8.50

ORDER FORM British Medical Journal, PO Box 295,
London WC1H 9TE, England *or any leading bookseller*

Please send me .... copy/copies of

☐ **HOW TO DO IT: 3**
☐ **HOW TO DO IT: 2**
☐ **HOW TO DO IT: 1**

Prices to include postage, by air abroad

NAME..
Please print name and address clearly
ADDRESS..
....
POST CODE...

☐ I enclose .... BMA Membership No. ....

Please make cheques payable to British Medical Journal or debit my credit card (*please tick box*)

☐ VISA ☐ AMERICAN EXPRESS ☐ MASTERCARD

CARD NUMBER ______________________________

Card expiry date..
Signature...
☐ Please send me a book catalogue

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors** **Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- **24 hour delivery.**
- **Courier services.**
- **Personal delivery.**

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia

Advancing The New Biology

A brighter start for dry eyes...
begins last thing at night
Used at night Lacri-lube soothes, protects and lubricates dry eyes for undisturbed sleep and comfort on waking.
LACRI–LUBE®
petrolatum mineral oil
OINTMENT
At the end of the day there's nothing quite like it for dry eyes
LACRI-LUBE®
S.O.P.
OPHTHALMIC OINTMENT
3.5 gm.
STERILE

Lacri-Lube Prescribing Information. Presentation: Sterile, bland, non-medicated ophthalmic ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. **Uses:** Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. **Dosage and administration:** For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. **Contra-indications etc:** No known contra-indications. **Pharmaceutical precautions:** Store away from heat. To avoid contamination during use, do not touch tip to any surface. **Legal Category:** P. **Package quantities:** Available in 3.5g ophthalmic tubes. **Basic NHS Cost:** (as at May 1987) £1.76. **Product Licence Number:** PL 0426/0041. **Product Authorisation Number:** PA 148/38/1 (Allergan Pharmaceuticals (I) Limited, Westport, Co Mayo).

ALLERGAN PHARMACEUTICALS
SCIENCE WITH VISION
Allergan Limited.
High Wycombe, Bucks. HP12 3SH

Full prescribing information is available on request. ®denotes registered trademark

21 DEC 1990
CENTRAL LIBRARY

22.4.91

OCTOBER 1990 VOL 74 NO 10

ucM

77

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial 577 Paget's disease and angioid streaks: one complication less? *Redmond Smith*

Original articles 579 Prevalence of angioid streaks and other ocular complications of Paget's disease of bone *T R Dabbs, K Skjodt*

583 How large must an iridotomy be? *B W Fleck*

589 A longitudinal study of children with a family history of strabismus: factors determining the incidence of strabismus *E Aurell, K Norrsell*

595 Retinal arterial macroaneurysms: risk factors and natural history *Robert W Panton, Morton F Goldberg, Marilyn D Farber*

601 The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma *John F Pitts, Jeffrey L Jay*

605 Effect of a β-blocker on altered body position: induced ocular hypertension *Dean A Smith, Graham E Trope*

607 A functional vagotomy induced by unilateral forced right nostril breathing decreases intraocular pressure in open and closed angle glaucoma *Joshua Backon, Nelson Matamoros, Manuel Ramirez, Rodrigo M Sanchez, Jaime Ferrer, Alberto Brown, Uriel Ticho*

610 Choroidal lesions in patients with AIDS *Marc A Rosenblatt, Carol Cunningham, Steven Teich, Alan H Friedman*

615 Therapeutic outcome of patients suffering from malignant melanomas of the conjunctiva *P K Lommatzsch, R E Lommatzsch, I Kirsch, P Fuhrmann*

Mini review 620 Endogenous posterior uveitis *J V Forrester*

Case reports 624 Malignant fibrous histiocytoma of the conjunctiva *Jacob Pe'er, Shmuel Levinger, Michael Ilsar, Harold Climenhaga, Elimelech Okon*

629 A case of cerebrotendinous xanthomatosis. II: the sterol content of a cataractous lens *P McKenna, S J Morgan, R C Bosanquet, M F Laker*

631 Histology of the lens in the Weill-Marchesani syndrome *Hisako Fujiwara, Yasushi Takigawa, Shinya Ueno, Kanshi Okuda*

635 Scleral melting in a patient with conjunctival rhinosporidiosis *R M L De Doncker, R J W de Keizer, J A Oosterhuis, A Maes*

638 Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy *A Hirsh, A Alhalel, A Weiss, H Brener, I Avni*

639 **Letters to the editor Notes 50 Years Ago**

CENTRAL LIBRARY

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE

Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Jou

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced*.

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof,
read it carefully for printers' errors. Alterati
original text should be kept to a minimum a
charged to the author.

REPRINTS may be ordered from the Publishin
when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Oph*
This publication is copyright under the Berne
and the International Copyright Convention.
reserved. Apart from any relaxations permi
national copyright laws, no part of this publicat
reproduced, stored in a retrieval system or trar
any form or by any means without the prior
of the copyright owners. Permission is not
required to copy abstracts of papers or of
condition that a full reference to the source
Multiple copying of the contents of the
without prior permission is always illegal.

NOTICE TO ADVERTISERS Applications for adv
space and for rates should be addressed to the
ment Manager, *British Journal of Ophthalmol*
House, Tavistock Square, London WC1H 9JR

NOTICE TO SUBSCRIBERS *British Journal of Ophth*
published monthly. The annual subscriptior
£106.00 inland and £126.00 overseas (US
Orders should be sent to the Subscription
British Journal of Ophthalmology, BM
Tavistock Square, London WC1H 9JR. Orde
be placed with any leading subscription agen
seller. (For the convenience of readers in
subscription orders with or without paymen
be sent to British Medical Journal, Box 560
bunkport, Maine 04046. All inquiries, howeve
addressed to the Publisher in London.) Subsc
pay for their subscriptions by Access, Visa, or
Express by quoting on their order the credit
card preferred together with the appropriat
account number and the expiry date of the
inquiries regarding air mail rates and single cop
published should be addressed to the Pu
London.

Second class postage paid, Rahway, NJ. Postm
address changes to: *British Journal of Ophthal*
Mercury Airfreight International Ltd Inc, 232
Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd

NIGHT WORKER.

Alcon's Maxitrol Ointment has been developed to provide
he same highly effective action against inflammation and
nfection as Maxitrol drops but with an added benefit.
It is ideal for overnight use.

Consequently, a patient's sleep need not be disturbed
whether in hospital or at home, because Maxitrol
goes on working through the night.

MAXIMISE
ON
MAXITROL®

Dexamethasone/Polymyxin B Sulphate/Neomycin Sulphate

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford,
Herts, WD2 4YR.
Telephone: 0923 246133 Fax: 0923 243331

PRESCRIBING INFORMATION:

RESENTATION: Dexamethasone Ph. Eur. 0.1% Polymyxin B Sulphate Ph. Eur. 6,000 units/g and Neomycin Sulphate
h. Eur. equivalent to Neomycin 3.5mg/g in an ointment base. **CLINICAL USES:** Management of infectious ocular
flammations produced by organisms which are sensitive to Neomycin Sulphate and Polymyxin B Sulphate. Acute or chronic
on-purulent conjunctivitis, blepharo-conjunctivitis, kerato-conjunctivitis, non-specific superficial keratitis, deep keratitis, and acne
sacea keratitis, herpes zoster ophthalmicus, iridocyclitis, mild acute iritis, recurrent marginal ulceration, corneal ulcer, non-purulent
epharitis, scleritis, episcleritis and sclero-conjunctivitis. Post-operatively to prevent ocular infection. **DOSAGE AND**
DMINISTRATION: Apply a small amount of ointment into the conjunctival sac, 3-6 times a day. When a favourable response is observed,
e dosage may be reduced to 3-4 applications per day. This may be followed by once a day applications for several more days.
ONTRA-INDICATIONS: This drug is contra-indicated in tuberculous, fungal and most viral lesions of the eye (herpes simplex/dendritic
eratitis); vaccinia; varicella; acute purulent conjunctivitis and acute purulent blepharitis; and in those persons who have shown hypersensitivity to
ny of its components. **WARNINGS:** Extended use of topical therapy may cause increased intraocular pressure in certain individuals. It is advisable
at intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of
opical steroids. Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If the condition does not respond within a
easonable period other forms of therapy should be instituted. Appropriate measures should be taken when this occurs. A few individuals may be sensitive to
ne or more components of this product. If any reactions indicating sensitivity are observed discontinue use. Extended use of topical steroids is a possible factor
the formation of subcapsular cataracts. **PREGNANCY WARNING:** Although topical steroids have not been reported to have an adverse effect on pregnancy,
e safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long term treatment of pregnant

USED TO TREAT
OVER 2 MILLION
PATIENTS

USED IN 153
COUNTRIES

OVER 1,000
CLINICAL PAPERS
PUBLISHED

WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most
cases clear on withdrawal. If seen, beta-blocke
should be withdrawn gradually.

Do not use in patients with soft contact lens
Mydriasis resulting from use of 'Timoptol' with adre
aline reported occasionally. Potentially, hypotensic
and/or marked bradycardia may result from additic
of 'Timoptol' to a calcium antagonist, rauwolf
alkaloid or beta-blocker.

Children: Not recommended. Data not available f
use in children. *Nursing:* Mother should either st
nursing or stop 'Timoptol'. *Pregnancy:* Not studie
weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, bleph

12-90 TOT.89.GB.4697.J.

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
)PEN-ANGLE GLAUCOMA
IERAPY BY THE MAJORITY
UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE

TOP 'TIMOPTOL'?

is, keratitis, blepharoptosis, and decreased corneal nsitivity. Visual disturbances, including refractory anges (due sometimes to withdrawal of miotics), plopia, and ptosis.
adycardia, arrhythmia, hypotension, syncope, art block, cerebrovascular accident, cerebral chaemia, congestive heart failure, palpitation, rdiac arrest.
onchospasm (predominantly with pre-existing onchospastic disease), respiratory failure, dyspnoea.
eadache, asthenia, nausea, dizziness, depression.
ypersensitivity, rash, and urticaria.
eactions with an unestablished relationship are CMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST
0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack. 0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

Product licence numbers:
0.25% Ophthalmic Solution 'Timoptol', 0025/0134.
0.5% Ophthalmic Solution 'Timoptol', 0025/0135.
® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference
1. Data on file, Merck Sharp & Dohme Limited.

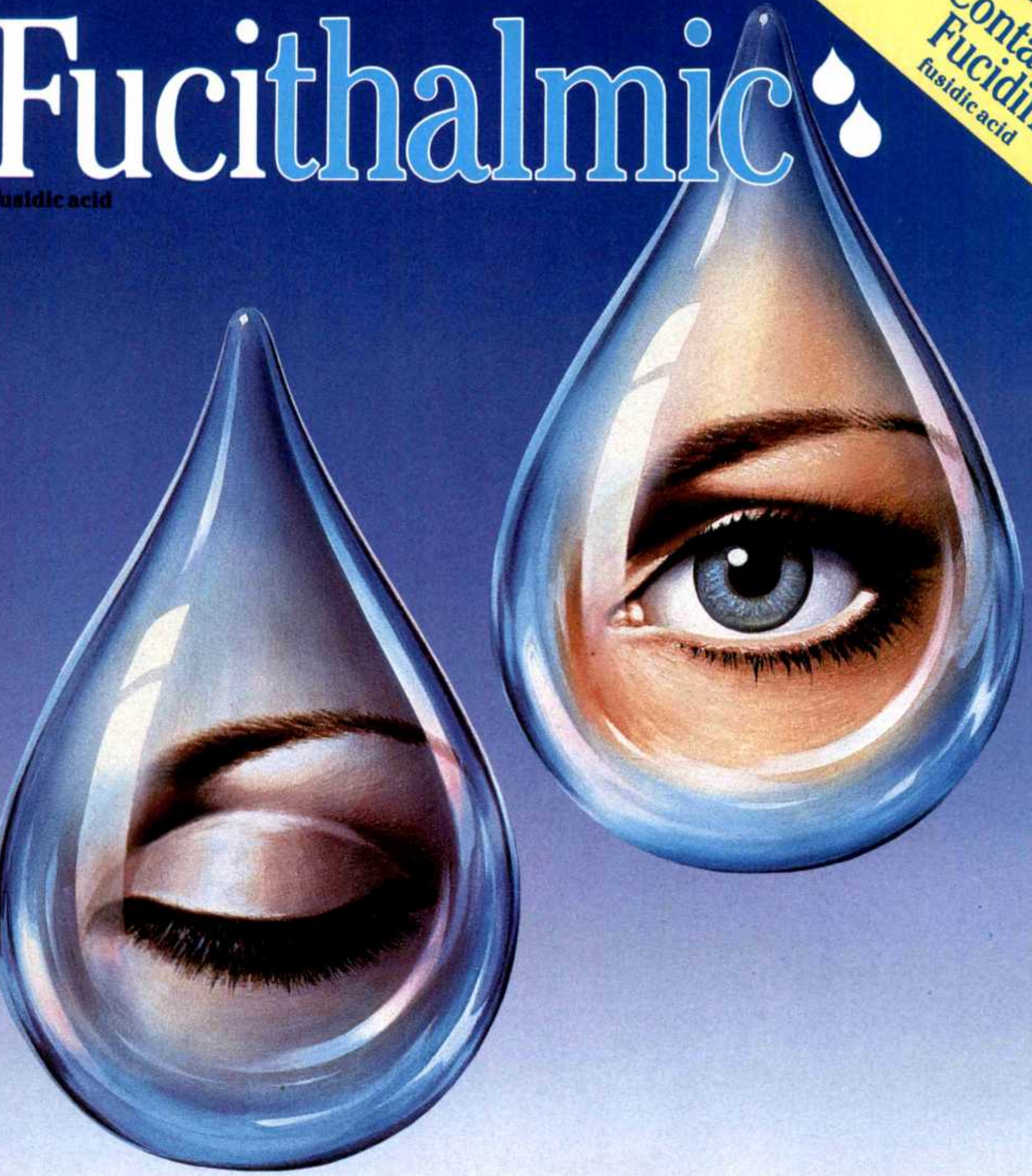
Ophthalmic Solution
Timoptol®
(timolol maleate, MSD)

JNSURPASSED AS FIRST-LINE GLAUCOMA THERAPY

Fucithalmic

fusidic acid

Contains Fucidin
fusidic acid



twice daily for bacterial conjunctivitis

▼ Prescribing Information.

Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses:** Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications:** Bacterial conjunctivitis due to sensitive organisms. **Dosage:** One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications:** Hypersensitivity to any component. **Precautions:** Should not be used when contact lenses are being worn. **Side effects:** Transient stinging. Hypersensitivity may occur. **Product Licence Number:** 0043/0137. **Basic N.H.S. Price:** £2.25/5g tube.

L E O

Further information available on request:

Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

British Journal of Ophthalmology, 1990, 74, 577–578

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Paget's disease and angioid streaks: one complication less?

One or two cherished pieces of ophthalmological folklore have been demolished recently. First there were the 'cholesterol crystals' of the Christmas tree cataract, shown by Hayes and Fisher[1] to be no such thing; next there was the association between pre-existing chronic glaucoma and central retinal vein occlusion,[2] and possibly now, in this month's issue of the *BJO*, the widely taught dictum of Paget's disease being associated with angioid streaks. One is worried about what may come next – perhaps some ophthalmological Illych[3] to tell us that holes in the retina are not associated with detachment or, dare I say it, that raised intraocular pressure has nothing to do with glaucoma.

Traditions in medical literature, whereby one generation of clinicians takes it upon trust that certain associations of symptoms and signs make up genuine syndromes may be difficult to trace back to their origins. This is not a problem with eponymous syndromes, since the original paper or papers should be easily traceable. But even this exercise sometimes leads to surprises, and one finds that the syndrome bearing the eponymous name is hardly mentioned in the original paper, or, as in the case of Graves' disease for example, the original communication was made at a meeting of a hospital society and not published at all (Graves' paper can be found only in an anthology of clinical lectures[4]). According to Duke-Elder[5] the association of Paget's disease with streaks was first pointed out by Batten in 1931[6] and by Verhoeff in the same year.[7] Unfortunately both these references are seriously flawed. Batten does not report a case of his own but merely writes that he has seen a fundus painting 'in Hamblin's collection of drawings' of a case of Frank Juler's which was said to have angioid streaks associated with Paget's disease. In the same paper Batten quotes Verhoeff: 'I have seen atypical case in a patient with Paget's disease of the skull but I am not prepared to say that it is of any special significance.' Unfortunately this is said to have been printed in a 'presession book' of the section of ophthalmology of the American Medical Association in 1928, but it does not seem to be available in the libraries I have access to. To make matters worse, the 1931 Verhoeff paper quoted by Duke-Elder is not about angioid streaks at all but about some entirely different fundus streaks resulting from choroidal detachment. Verhoeff even makes a point of emphasising that they are not angioid streaks. Thus, correctly as far as I can see, the most commonly quoted first description is usually that of Terry,[8] as pointed out by Dabbs and Skjodt in their article. If Terry's four examples of angioid streaks out of 50 cases of Paget's were really definite, as he claims, it would be impossible to dismiss such an association of two such rare conditions as occurring by chance alone. But if one searches the literature, say for the years 1950 to 1980, one constantly meets allusions to the association, with few fresh cases being reported, rather like the Batten-Verhoeff fiasco. So the suspicion begins to creep in that perhaps there was something not quite right with Terry's own observations and what we have been experiencing is the phenomenon of perpetuating a medical rumour.

It is of considerable interest that, in the paper by Shields and colleagues,[9] of 56 patients with angioid streaks seen during a period of seven years not a single one was suffering from Paget's disease, whereas no fewer than 30 had pseudoxanthoma elasticum. The literature abounds with case reports of angioid streaks most of which are entitled 'Two cases of the Grönblad-Strandberg syndrome,' but when the ocular associations with Paget's disease are mentioned it is usually in the context of compressive lesions of the optic nerve due to bony changes in the skull. One begins to suspect therefore that Dabbs and Skjodt might be correct in their conclusion that Paget's disease is only infrequently associated with angioid streaks, to put it mildly.

A paper which is not often cited is that of Mazalton and colleagues,[10] which reports a case in which Paget's disease and the Grönblad-Strandberg syndrome occurred in the same patient. The authors also reported that four other cases had been described previously. It was not entirely clear whether angioid streaks were seen in their particular case, but, given that they seem to occur in around 80% of cases of the Grönblad-Strandberg syndrome[11] and that the case being described had a haemorrhagic retinopathy, it is likely that streaks were present. A boost to Terry's theory is given in a paper from the Mayo Clinic[11] in which precise percentages are given of patients with pseudoxanthoma elasticum (PXE) alone or PXE plus streaks and streaks alone or streaks combined with Paget's disease. Whereas 63 of a total of 74 PXE cases had streaks, only two out of 32 cases of Paget's disease had streaks – that is, around 6% – not far out of line with Terry's 8%. Thus one's original suspicion that the Paget's-angioid streaks association was just another piece of ophthalmological folklore about to be disproved turns out not to be justified. Added confirmation that there is probably some truth in the story is given by Gass and Clarkson.[12] They followed up a case to necropsy and describe not only the clinical features but the histopathological changes in Bruch's membrane. There is only one defect in this paper and that is the published fundus photographs of the streaks, which are not entirely sharp. However, this is not a serious criticism, since it is noticeable that fundus photographs in which streaks are alleged to show are often rather unconvincing. It appears that angioid streaks are not photogenic. The validity of a claim depends entirely on the opinion of the observer as to what is or is not an angioid streak on ophthalmoscopy; it is not possible to be certain one way or the other.

One can finally conclude that the coincidence of angioid streaks with Paget's disease certainly does occur but perhaps not as often as some clinicians seem to think, and the streaks are far more likely to be found in the Grönblad-Strandberg syndrome (PXE) (not to mention one or two other conditions, not the subject of this editorial). Finally it has to be said that, if Paget's disease can coexist with PXE, a case of Paget's disease with streaks should obviously be very carefully examined to exclude PXE; and, who knows, the pure Paget's-streaks association might yet turn out to be false.

REDMOND SMITH

1 Hayes BP, Fisher RF. Ultrastructural appearances of a lens with marked polychromatic lustre evidence for diffraction as a cause *Br J Ophthalmol* 1984; 68: 850–8

2 Cole MD, Dodson PM, Hendeles S. Medical conditions underlying retinal vein occlusion in patients with glaucoma or ocular hypertension. *Br J Ophthalmol* 1989; 73: 693–8.

3 Illych I. *Medical Nemesis the expropriation of health* London Calder and Boyars, 1975

4 Graves RJ. *Collected clinical lectures*. Philadelphia Waldie, 1838

5 Duke-Elder WS. *Textbook of ophthalmology* London· Kimpton, 1940; 3: 2413–8.

6 Batten RD. Angioid streaks and their relation to a form of central choroidal disease *Br J Ophthalmol* 1931; 15: 279–89.

7 Verhoeff FH The nature and origin of the pigmented streaks caused by the separation of the choroid. *JAMA* 1931; 97: 1873–6.

8 Terry TT. Angioid streaks and osteitis deformans *Trans Am Ophthalmol Soc* 1934, 32: 555–73

9 Shields JA, Federman JL, Tomer TL, Annesley WH Jnr Angioid streaks *Br J Ophthalmol* 1975; 59: 257–66

10 Mazalton A, Messing R Maladie de Paget et syndrome de Gronblad-Strandberg. *Sem Hop Paris* 1961, 37: 3591–6

11 Connor PJ Jnr, Juergens JL, Perry HO, Hollenhurst RW, Edwards JE. Pseudo-xanthoma elasticum and angioid streaks a review of 106 cases *Am J Med* 1961, 30: 537–43

12 Gass JDM, Clarkson JG Angioid streaks and disciform macular detachment in Paget's disease (osteitis deformans) *Am J Ophthalmol* 1973, 75· 576–86

British Journal of Ophthalmology, 1990, 74, 579–582

ORIGINAL ARTICLES

Prevalence of angioid streaks and other ocular complications of Paget's disease of bone

T R Dabbs, K Skjodt

Abstract

Seventy randomly selected patients with Paget's disease of bone were examined for ocular complications. The prevalence of macular degeneration and cataract was 24·3%. Only one patient was found to have angioid streaks. Eight patients had peripapillary chorioretinal atrophy. These findings suggest that the prevalence of serious ocular complications of Paget's disease is not as high as previously thought. The significance of peripapillary chorioretinal atrophy requires further evaluation.

Paget's disease has been recognised as having ocular sequelae since James Paget's original description of the disorder in 1877. [1] The complications may be divided into two main groups; those intrinsic to the eye, and those resulting from compression of the orbital contents or sensory and motor nerves supplying the eye and adnexae. The intrinsic disorders reported are corneal opacities, cataract, angioid streaks, and disciform macular degeneration. Those conditions due to compression include papilloedema, optic atrophy, extraocular muscle palsies, exophthalmos, and nasolacrimal duct obstruction.[2] The mechanisms by which compressive lesions exert their effects are easily understood but not so the intrinsic lesions. From the ophthalmological standpoint angioid streaks are the lesions which attract most attention because of their potential for producing sight-threatening subretinal neovascular membranes, which are treatable in appropriate circumstances.[3] Accurate data on the prevalence of these ocular complications and in particular angioid streaks are obviously of importance in the management of Paget's disease.

Angioid streaks were originally described by Doyne in 1889.[4] Paget's disease was first observed as an association by Terry in 1934.[5] After studying 50 cases he identified four with 'definite angioid streaks'. From this finding he concluded the 'The coexistence of angioid streaks and osteitis deformans is of too frequent occurrence to be the result of chance alone'. Several reports have since confirmed the presence of angioid streaks in cases of proved Paget's disease. The prevalence has been placed at somewhere between 8% and 15%.[6,7] The only recent survey undertaken which had the advantage of employing fluorescein angiography to detect angioid streaks was carried out by Clarkson and Altman in 1982.[8] They examined 50 selected sufferers from Paget's disease and performed fluorescein angiography on every patient, discovering five cases of angioid streaks, placing the prevalence at 10%.

Necropsy evidence of Paget's disease suggests an overall prevalence of 3% in the population aged over 40, rising to 9% in those aged over 80.[9,10] From these figures it has been estimated that there are approximately 750 000 people in the UK with Paget's disease. This would suggest that the number with angioid streaks is between 60 000 (8%) and 112 500 (15%).

In view of these findings Paget's disease might be expected to account for a considerable number of patients with ocular disease, particularly macular degeneration. But on clinical grounds Paget's appears to feature very infrequently as a cause of ocular problems in everyday practice. In order to evaluate the prevalence and nature of retinal and other ocular disorders in Paget's disease a study of randomly selected patients was undertaken.

Patients and methods

The patients were recruited from inpatients and outpatients attending the Regional Metabolic Unit at the Royal Hallamshire Hospital, Sheffield. The group of patients approached were attending for the purposes of a separate investigation into their past exposure to canine distemper. All patients were offered an ophthalmic examination and were advised about the aims of the project. Seventy patients were included in the study. All had radiologically proved Paget's disease, the diagnosis being confirmed by iliac crest bone biopsy. Every patient had pain, with or without deformity, and was receiving treatment accordingly.

Each patient was interviewed and a full history obtained. An ocular examination was undertaken, including refraction slit-lamp biomicroscopy, tonometry, confrontation fields, and funduscopy after pupillary dilatation. When a significant retinal abnormality was discovered, fluorescein angiography was performed. The risks involved in performing angiography in asymptomatic subjects without identifiable retinal lesions was considered to be unjustifiable. Sixteen patients underwent fluorescein angiography, and all were reviewed separately by two ophthalmologists. The diagnosis of angioid streaks was made according to the criteria

Birmingham and Midland Eye Hospital, Church Street, Birmingham B3 2NS
T R Dabbs

Eye Department, Hvidovre University Hospital, Kettegaards alle, 2650 Hvidovre, Denmark
K Skjodt

Correspondence to
T R Dabbs, FRCS

Accepted for publication
22 March 1990

Table 1 Comparison of patients with and without peripapillary atrophy

	With PPA (n=8)	*Without PPA (n=61)*	*Significance*
Age mean (SD)	71·98 (8·98)	71·88 (9·55)	NS*
Duration			
Median (range)	16 (1–46)	6 (0·16–30)	NS†
Average VA‡	2·75 (1·5–5·5)	2 (1–8)	NS†

*Two-sample *t* test. †Wilcoxon rank sum test.

‡VA	6/6	6/9	6/12	6/18	6/24	6/36	6/60	CF	HM	PL	NPL
Code	1	2	3	4	5	6	7	8	9	10	11

Table 2 Prevalence of macular degeneration and cataract

	Total no. of eyes affected	*Disease in one or both eyes*	*Prevalence %*
Cataract	31	17	24·28
Macular degeneration	25	17	24·28

described by Shields *et al.*[11] Accordingly, linear, variably coloured lesions present at the level of Bruch's membrane were being sought during fundus examination. The fluorescein angiograms were scrutinised for the presence of directly fluorescing streaks or those showing hyperfluorescent borders during the later phases of angiography.

Statistical analysis was performed with the MINITAB software package and comprised the χ^2 test for categorical variables and the two-sample t test for continuous variables. When continuous variables were skewed, the non-parametric Wilcoxon rank sum test was employed.

Results

Seventy patients were entered into the study. There were equal numbers of males and females. The age range was 49 to 88 years, mean 71·6 years. The duration of disease ranged from two months to 46 years, mean 8·2 years.

The sites affected were divided into four categories: pelvis, head, axial skeleton, and limbs. The number of patients with one affected region was 33, two sites 20, and three sites, 17. No patient had disease in all four sites.

Visual acuity was noted and divided into 11 groups as shown in Table 1. In order to compare the visual performance of our group with those of other epidemiological studies the prevalence of macular degeneration and cataract was evaluated in accordance with the criteria adopted by the Framingham Eye Study in the following ways.[12] The presence of cataract judged to account for a visual acuity of 6/9 or less was recorded. Macular degeneration was identified as the 'dry' type, such as pigment disturbance or drusen formation, and of the exudative type with elevation of the retinal pigment epithelium or neurosensory retina. If these were detected, senile macular degeneration was diagnosed provided the visual acuity was 6/9 or worse.

Macular degeneration and cataract were found to be equally prevalent, as shown in Table 2. In only one case was the visual acuity reduced sufficiently to warrant blind registration; the cause being bilateral cataract.

The retinal findings were as follows:

Peripapillary chorioretinal atrophy. This was seen in 16 eyes of eight patients. Six of these patients underwent fluorescein angiography; two refused this test. The choriocapillaris and the retinal pigment epithelium appeared to be deficient in the immediate peripapillary zone, leading to hyperfluorescence on fluorescein angiography. The width of this hyperfluorescent ring was judged to be abnormally large. A typical example of peripapillary atrophy is shown in Figs 1 A, B.

This group of patients with peripapillary atrophy was compared with the rest of the study population with regard to age, visual acuity, and duration of Paget's disease. No statistically significant differences could be detected. An attempt was made at correlating the number and type of sites affected with the presence of peripapillary atrophy, but the number of cases was too small to show any statistically viable associations. It is, however, notable that of patients having the disease for more than 15 years (15 of 70) 1/3 were accounted for by patients with peripapillary atrophy (Table I).

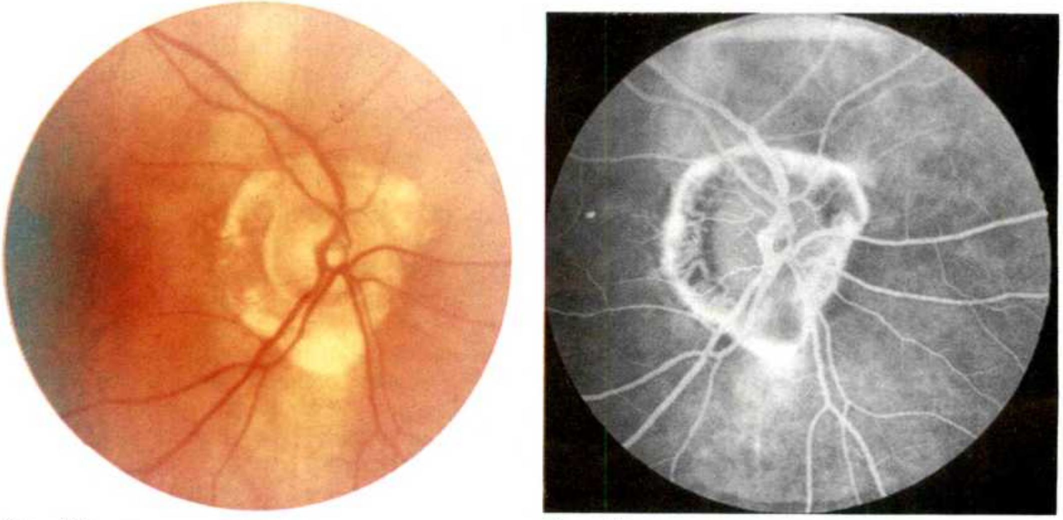


Figure 1A

Figure 1B

Figure 1 Colour photograph (A) and a fluorescein angiogram (B) of the right eye of a patient with peripapillary atrophy. The hyperfluorescent area visible inferior to the disc was not regarded as sufficiently well defined to qualify as an angioid streak. This subject is an 82-year-old woman with Paget's disease of 46 years' duration affecting three principal sites.

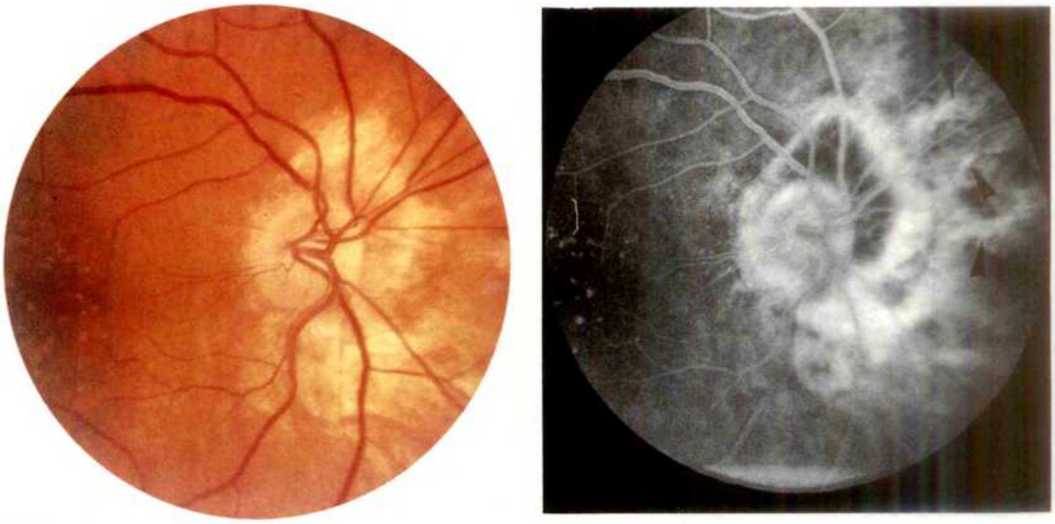


Figure 2A *Figure 2B*

Figure 2 Colour photograph (A) and a fluorescein angiogram (B) of the right eye of the single patient judged to have angioid streaks. The hyperfluorescent linear lesions radiating from the ring of peripapillary atrophy, though atypical, were thought to represent individual streaks (arrowed).

Angioid streaks. Both eyes of one patient showed marked peripapillary chorioretinal atrophy with linear extentions radiating a short distance peripherally (Figs 2 A, B). Although not typical, the angiographic appearance was thought to be consistent with angioid streaks. This patient also had macular drusen and atrophic macular degeneration affecting both eyes, the left being more severely affected. The patient, a man, was 69 and had had Paget's disease for eight years; it affected his pelvis, spine, and both legs. His visual acuities were 6/9 in the right eye and 6/60 in the left. He had no signs of pseudoxanthoma elasticum; a skin biopsy was not performed. This one patient represents an overall prevalence of 1·4% for angioid streaks in the series under study.

Peau d'orange was not identified in any case studied.

Compression of ocular cranial nerves was not identified, but one patient had considerable distortion of one orbit leading to downward displacement of the left globe. Fortunately there was no associated diplopia or optic nerve compression. Other conditions causing visual problems were chronic open-angle glaucoma in one patient, amblyopia in one eye, persistent untreatable retinal detachment in another, and bilateral cystoid macular oedema following intracapsular cataract surgery in a further patient. No cases of corneal dystrophy were discovered.

Discussion

The principal finding of this study was the low prevalence of angioid streaks (1·4%). The explanations probably lies in the method of patient selection and examination. Our group was randomly selected, and the severity of their disease was variable. In their survey Clarkson and Altman[8] selected patients with severe disease. Earlier studies may have tended to include patients with more advanced disease, as the increased availability of radiography and biochemical analysis now allow for earlier detection of Paget's disease.

With the exception of the studies by Terry[5] and Clarkson and Altman[8] none have been carried out by one investigating team on a group of Paget's sufferers; the reported prevalences were arrived at by collecting cases from several sources, thus potentially leading to inaccurate estimates.[6,7]

Peripapillary chorioretinal atrophy has been described in other conditions associated with angioid streaks and is regarded as a precursor of angioid streaks.[7,11] The only previous estimate of the frequency of peripapillary atrophy was that of Terry at 18%.[5] We detected it in eight out of 70 (11·5%).

The definition of peripapillary atrophy is somewhat inexact. Fluorescein angiography is of little help, as there is no information as to the extent of normal peripapillary hyperfluorescence. Peripapillary changes occur in myopia, presumed ocular histoplasmosis, and peripapillary choroidal sclerosis, and are said to occur as a consequence of aging.[11,13]

None of our patients were myopic, nor were there any signs of presumed ocular histoplasmosis.

Choroidal sclerosis is regarded as being difficult to separate from the peripapillary changes in angioid streaks, and according to Krill and Archer peripapillary choroidal sclerosis may progress to angioid streaks, further indicating a considerable degree of overlap between the two conditions.[11,14] Some of our patients may therefore have been cases of peripapillary choroidal sclerosis, or in some cases their condition may have been due to age alone.

We attempted to identify any factors separating patients with peripapillary atrophy from the rest of the subjects, but no statistically significant result was forthcoming.

One-third of the patients with a disease duration of 15 years or more were accounted for by this group. Peripapillary atrophy might be related to the duration of Paget' disease, but a larger study is needed to prove this statistically.

Our subjects did not have an excess of serious ocular disease. The prevalence of 24·3% for macular degeneration compares favourably with previous studies of eye disease in the elderly. The most demographically comparable study carried out by Gibson *et al* in Melton Mowbray using the Framingham criteria, detected a prevalence of 38·8% in a significantly older group of patients.[15]

The prevalence of cataract at 24·3% is significantly lower than the findings of the Melton Mowbray study (41·6%). This also is at variance with earlier reports of an increased incidence of cataract in sufferers from Paget's disease.[16]

The age difference between the group under study and other studies makes direct comparison difficult. Nevertheless it seems that there is not an increased risk of the development of sight threatening disease in the population from which our study group was drawn.

We conclude that Paget's disease is only infrequently associated with angioid streaks, and confers no excess risk of serious eye disease. The existence of peripapillary atrophy was noted in eight patients and is probably related to the duration of the disease. This relationship requires further study for clarification.

We thank Dr J A Kanis for allowing us to study his patients, Mr J Gibson and Mr J Talbot for their help with interpretation of the fluorescein angiograms and Mr D Shaw for undertaking the statistical analyses.

1 Paget J. Remarks on osteitis deformans. *Illustrated Medical News* 1989; **2:** 181–2.
2 Hamdy RC. *Paget's disease of bone: assessment and management.* Armour Pharmaceutical Company (Praeger, UK), 1981: 57–8.
3 Deutman AF, Kovaks B. Argon laser treatment in complications of angioid streaks. *Am J Ophthalmol* 1979; **88:** 13–7.
4 Doyne RW. Choroidal and retinal changes – the result of blows to the eye. *Trans Ophthalmol Soc UK* 1889; **9:** 128–40.
5 Terry TT. Angioid streaks and osteitis deformans *Trans Am Ophthalmol Soc* 1934; **32:** 555–73.
6 Paton D. *The relation of angioid streaks to systemic disease.* Springfield: Thomas, 1972; 20–41.
7 Sholtz RO. Angioid streaks. *Arch Ophthalmol* 1941; **26:** 677–93.
8 Clarkson JG, Altman RD. Angioid streaks. *Surv Ophthalmol* 1882; **26:** 235–46.
9 Schmorl G. Über Osteitus deformans Paget. *Virchows Arch (A)* 1932; **283:** 694–751.
10 Collins DH. Paget's disease of bone – incidence and subclinical forms. *Lancet* 1956; ii: 51–7.
11 Shields JA, Federman JL, Tomer TL, Annesley WH. Angioid streaks: 1. Ophthalmoscopic variations and diagnostic problems. *Br J Ophthalmol* 1975; **59:** 257–64.
12 Khan HA, Liebowitz HM, Ganley JP, *et al.* The Framingham Eye Study. 1. Outline and major prevalence findings. *Am J Epidemiol* 1977; **106:** 17–32.
13 Stafford WR. *Clinical ophthalmology.* Hagerstown: Harper and Row, 1988; **4:** chapter 66: 1–2.
14 Krill AE, Archer D. Classification of the choroidal atrophies. *Am J Ophthalmol* 1971; **72:** 562–85.
15 Gibson JM, Rosenthal AR, Lavery J. A study of the prevalence of eye disease in the elderly in an English community. *Trans Ophthalmol Soc UK* 1985; **104:** 196–203.
16 Zion VM, Billet E. *Clinical ophthalmology.* Hagerstown: Harper and Row, 1988; **5:** chapter 29: 13–5.

OH DEAR,
I FORGOT TO TAKE ALL MY DROPS
AGAIN.

What can you give a patient who suffers from amnesia as well as glaucoma?

Getting patients to comply with complicated ose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, he beta blocker most patients only need to take nce a day. This is possible because of Betagan's ustained activity over 24 hours,[1] hich has been shown to be ffective in controlling the ntraocular pressure of up to 1% of patients on a once aily dose.[2]

In fact, in a study evaluating once-daily Betagan the authors concluded "once-daily treatment with levobunolol appeared to be as effective as twice-daily treatment while offering greater convenience and comfort and potentially greater safety."[3] So next time you're looking for a simple but flexible treatment for open angle glaucoma, consider Betagan.

It's a name worth remembering.

NEW

BETAGAN®

(levobunolol hydrochloride 0.5%)

ONCE DAILY

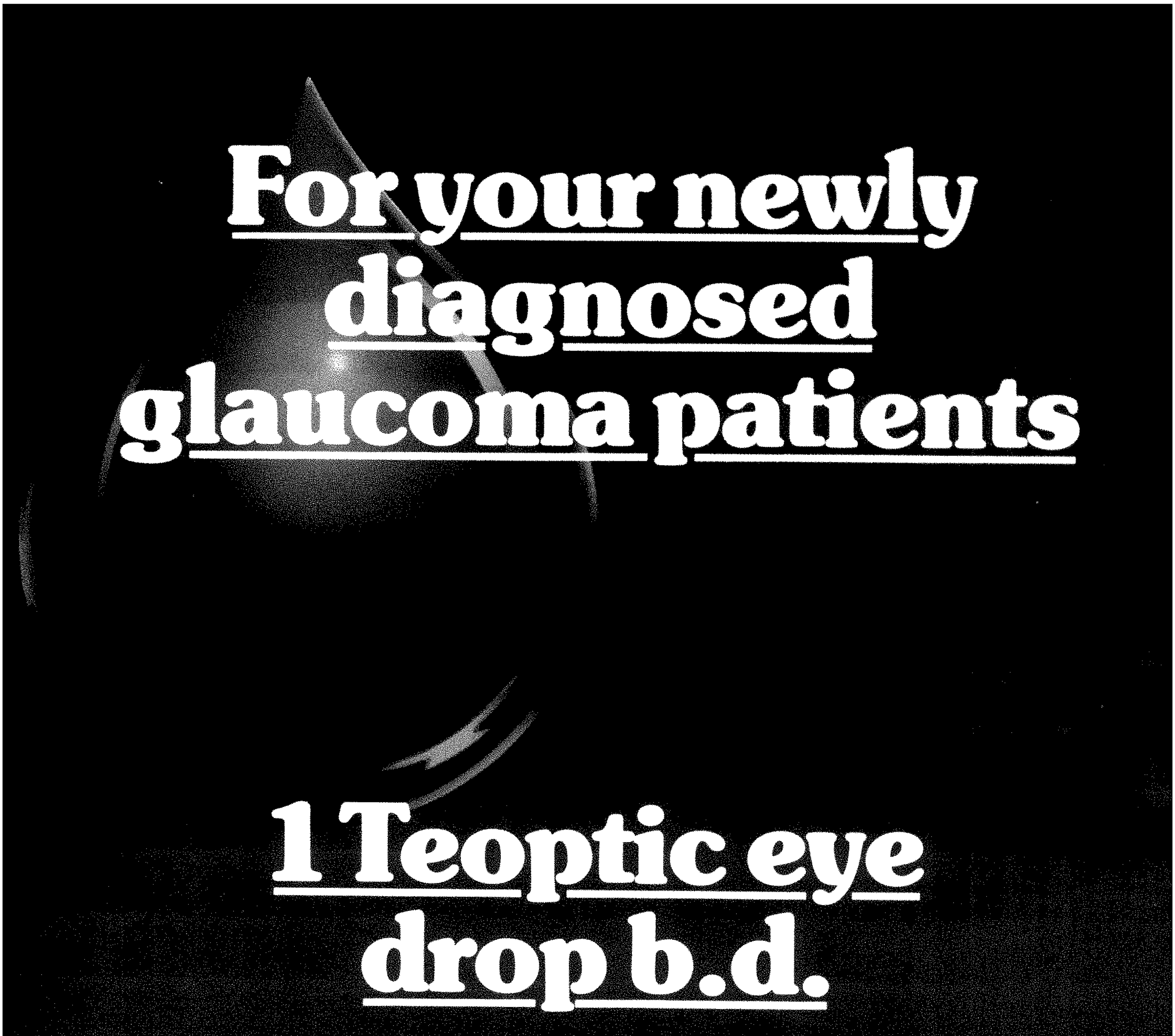
ONE DROP THEY WON'T FORGET

PRESCRIBING INFORMATION

RESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v). **ACTION:** Beta-adrenergic blocking agent. **INDICATIONS:** Reduction of traocular pressure in chronic open-angle glaucoma and ocular hypertension. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:** Contraindications: Bronchial sthma; history of bronchial asthma; chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block; cardiac failure; cardiogenic ock; hypersensitivity to any component. Caution in labile diabetes and in patients receiving oral beta-adrenergic blocking agents. Do not use in patients continuing to wear ydrophilic (soft) contact lenses. Transient ocular burning and stinging on instillation may occur. Bradycardia, ypotension, dyspnoea and asthma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) nce or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE:** £5.05 L 0426/0060. Full prescribing information is available on request.

Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11. . Wandel, T. *et al.*, Am J Ophthalmol 1986; *101*: 298-304.

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.
® Betagan is a registered trade mark.


For your newly diagnosed glaucoma patients
1 Teoptic eye drop b.d.

References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

Teoptic: Abbreviated prescribing information

Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity. **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

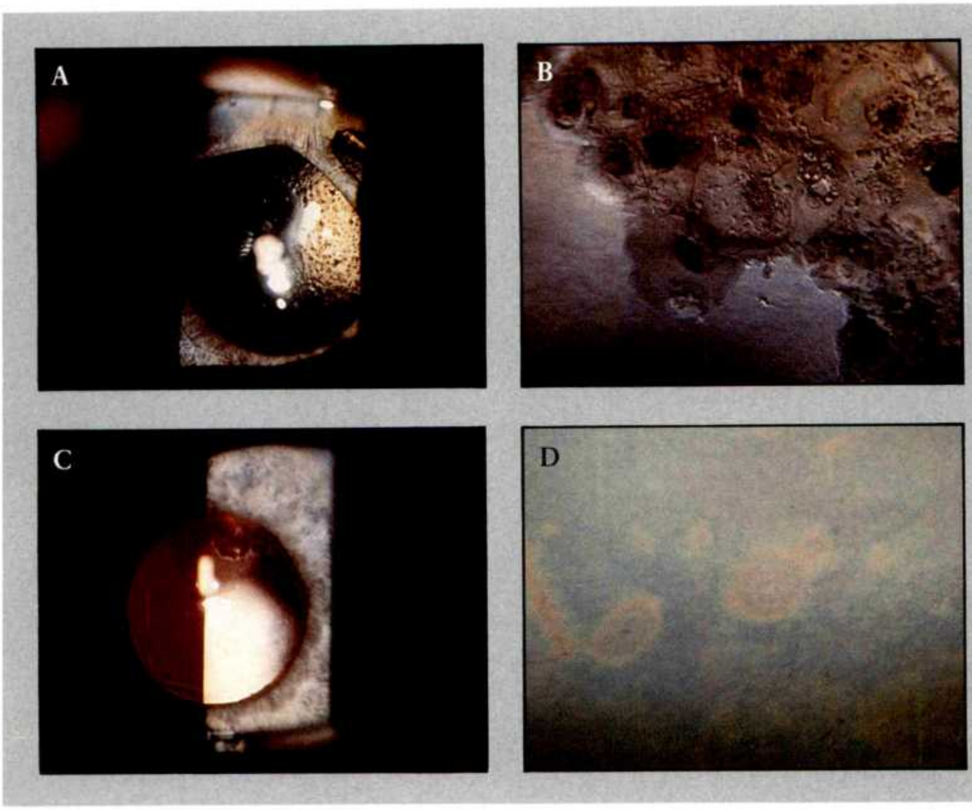
- Effectively lowers IOP[1]
- Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol *[2,3]
- Has a prolonged therapeutic effect[4] thus offering flexible b.d. dosage regimen
- Well tolerated with few local side-effects[5]
- Low concentration of benzalkonium chloride in a buffered solution.

* Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.

Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.
Teoptic is under licence from Otsuka, Japan.
Further information is available on request to the above address.

Comparison between Heparin surface modified IOLs and normal IOLs in the same patient.



This female has a history of longstanding diabetes and glaucoma.

A. Slit lamp
B. Specular microscopy

Right eye — NORMAL PMMA LENS

- 11 months post-operatively
- Confluent giant cells can be seen clearly on both slides

C. Slit lamp
D. Specular microscopy

Left eye — HEPARIN SURFACE MODIFIED LENS

- 6 months post-operatively
- No giant cells
- Newton's rings seen clearly

A clear case for Heparin surface modified IOLs.

Pharmacia Limited,
Ophthalmics Division, Pharmacia House, Midsummer Boulevard, Milton Keynes MK9 3HP.
Telephone: (0908) 661101. Telex: 826778. Fax: (0908) 690091

Pharmacia

British Journal of Ophthalmology, 1990, 74, 583–588

How large must an iridotomy be?

B W Fleck

Abstract

Four cases of acute angle closure glaucoma in eyes with a small but patent Nd-YAG laser iridotomy are presented, and similar cases in the literature are reviewed. Theoretically a 15 µm diameter iridotomy should be large enough to prevent angle closure glaucoma due to pupil block. Mechanisms by which larger iridotomies fail to prevent angle closure glaucoma, and the role of provocation tests following iridotomy, are discussed. An iridotomy should be at least 150–200 µm in diameter if acute angle closure glaucoma is to be reliably prevented.

Various forms of iris surgery have been used to treat angle closure glaucoma since von Graefe's original description of the broad iridectomy in 1857.[1] Surgical iridotomy was introduced by Curran in 1920.[2-4] Peripheral iridectomy was described by Chandler in 1952.[5] Argon laser iridotomy,[6] and more recently Nd-YAG laser iridotomy,[7] have already largely superseded surgical iridectomy. While laser surgery has many advantages over conventional surgery, it must not be forgotten that laser iridotomy represents a return to the use of smaller iris openings than those obtained by surgical peripheral iridectomy.[8] Gifford noted in 1921 that very small surgical iridotomies were not as effective in controlling intraocular pressure as larger iridotomies.[4]

Reports are now emerging of acute angle closure glaucoma developing in the presence of a small but patent argon[9 10] or Nd-YAG[11 12] laser iridotomy. While cases of acute angle closure glaucoma following surgical peripheral iridectomy have generally been attributed to plateau iris syndrome,[13-15] not all cases of acute angle closure glaucoma following a small laser iridotomy can be placed in this category.[9-12] We have treated four patients who developed acute angle closure glaucoma despite the presence of a patent Nd-YAG laser iridotomy.

The mechanism of failure of very small iridotomies may be related to obstruction of aqueous flow at very small iridotomy size. Below a critical surface area significant iris bombé may occur at normal aqueous flow rates. When iris bombé is sufficient to cause iridocorneal contact throughout a critical extent of the angle, beginning superiorly, acute angle closure glaucoma results.[16 17] The minimum 'safe' size of iridotomy has not been defined, but an approximate value may be calculated from a simple mathematical model.

Department of Ophthalmology, Royal Infirmary, Edinburgh EH3 9HA
B W Fleck

Correspondence to
B W Fleck, FRCSEd,
Princess Alexandra Eye Pavilion, Chalmers Street,
Edinburgh EH3 9HA

Accepted for publication
11 April 1990

Material and methods

We are undertaking a prospective randomised comparison of Nd-YAG laser iridotomy and surgical peripheral iridectomy in the treatment of acute angle closure glaucoma. The cases presented belong to the laser treated group in this study.

A Zeiss Visulas Nd-YAG laser and Zeiss anterior segment YAG contact lens were used in all treatments. Patients were given acetazolamide 500 mg orally one hour before treatment, and one pilocarpine eyedrop 2% 30 minutes before treatment.

A treatment site was chosen in the superior iris between 10 and 2 o'clock, approximately two-thirds of the distance from the pupil margin to the base of the iris. An iris crypt was used, when present. A single 5–10 mJ pulse was delivered to the treatment site. If this pulse did not penetrate the iris, further single pulses were delivered to the same site until penetration was achieved. A gush of aqueous fluid from the posterior chamber could be seen at the moment of penetration. Patency was assessed by direct observation of the posterior chamber or anterior lens capsule.

The size of iridotomies was measured by comparison with the 0·2 mm spot produced by a Haag-Streit slit-lamp focused on the iris plane.

Results: case reports

CASE 1

A 75-year-old hypermetropic man presented with right acute angle closure glaucoma of 48 hours' duration. The intraocular pressure was 78 mmHg, the anterior chamber was shallow, and the angle was closed throughout 360°. The left eye had a very narrow, open angle. Treatment with acetazolamide 500 mg intravenously and pilocarpine eyedrops 2% hourly resulted in a fall in intraocular pressure to 12 mmHg, with an open angle throughout 360°. Nd-YAG laser iridotomy was performed three days later. A treatment site 1 mm from the limbus at 10 o'clock was chosen. The iris was a light grey colour, with no crypts. Three 9·0 mJ pulses resulted in a small (200×100 µm) patent iridotomy. Minimal iris bleeding occurred at the time of treatment, but there were no other complications. One week after treatment the iridotomy was patent, though small. The intraocular pressure was 10 mmHg. No further eye medication was prescribed.

Two weeks after treatment the patient complained of blurred vision in the right eye. The intraocular pressure was 68 mmHg, and gonioscopy revealed 300° of angle closure superiorly. Medical treatment with topical pilocarpine 2% and timolol 0·5% reduced the intraocular pressure to 13 mmHg, with an open angle. The iridotomy was small (50×100 µm) but patent. Trabeculectomy with peripheral iridectomy was performed, leading to an intraocular pressure of 10 mmHg, and 6/5 visual acuity.

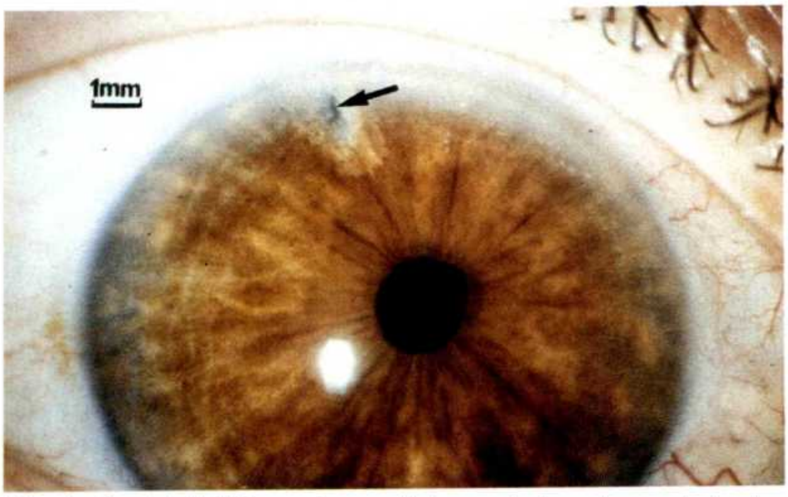


Figure 1 Case 2. Initial iridotomy size too small. Acute angle closure glaucoma developed. Iridotomy diameter 50 μm. The arrow indicates the very small area of full thickness opening at the centre of the treatment site.

CASE 2

A 65-year-old woman presented with left acute angle closure glaucoma of 24 hours' duration. The intraocular pressure was 58 mmHg, the anterior chamber was shallow, and the angle was closed throughout 360°. The right anterior chamber was shallow, with 120° of angle closure superiorly, and the intraocular pressure was 15 mmHg.

After initial medical control left trabeculectomy was performed.

Further examination of the right eye after treatment with pilocarpine eyedrops 2% revealed an open angle throughout 360°. Right Nd-YAG laser iridotomy was performed. The treatment site was 1 mm from the limbus, at 10 o'clock. The iris was brown, with no crypts. Four 9·7 mJ pulses were used to produce a patent iridotomy, and a further single 9·7 mJ pulse was used to enlarge the opening.

One week later the iridotomy was patent, though small. The intraocular pressure was 14 mmHg. At review three weeks later the right intraocular pressure was found to be 41 mmHg, and the pupil was dilated. Gonioscopy was not performed. The patient had been using cyclopentolate 1% drops to the left eye, and may have inadvertently contaminated the right eye. After treatment with pilocarpine eyedrops 2% the intraocular pressure returned to 16 mmHg. The iridotomy was patent, but small – 50×50 μm (Fig 1). Further laser treatment was given to enlarge the opening. Five 2·0 mJ Nd-YAG pulses were delivered to the sides of the existing iridotomy, enlarging the opening to 100×100 μm. After this treatment, eyedrops of Betamethasone 0·1% four times a day and tropicamide 1% once daily were prescribed. The patient returned four days later complaining of pain and reduced vision in the right eye. The intraocular pressure was 50 mmHg, and the pupil was mid-dilated and unreactive. The iridotomy was now situated very peripherally, with iris strands running forwards to the cornea, but appeared to be patent. Gonioscopy was not performed. The intraocular pressure returned to normal after treatment with acetazolamide 500 mg intravenously, and pilocarpine eyedrops 2% hourly. The iridotomy was patent, but small (100×100 μm). The angle was open on gonioscopy. Treatment with pilocarpine eyedrops 2% four times a day was prescribed.

A pilocarpine/phenylephrine provocation test as described by Mapstone[18] was performed on the right eye one week later and was negative.

Intermittent aching pain above the right eye continued, and further Nd-YAG laser enlargement of the iridotomy was performed six weeks later. Twenty-one 1·1 mJ pulses were delivered by means of a Wise 103-dioptre contact lens, resulting in some oozing of blood. A further 10 1·0 mJ pulses were delivered 30 minutes later. The resulting iridotomy measured 200×200 μm.

One week later all symptoms had resolved, and the iridotomy measured 100×200 μm. Pilocarpine/phenylephrine testing was again negative. However, provocation with Tropicamide eyedrops 1% produced a rise of 9 mmHg in IOP, with folds of iris blocking the trabecular meshwork over 270° on gonioscopy. At follow-up three weeks later the intraocular pressure was 17 mmHg, with no medication (Fig 2).

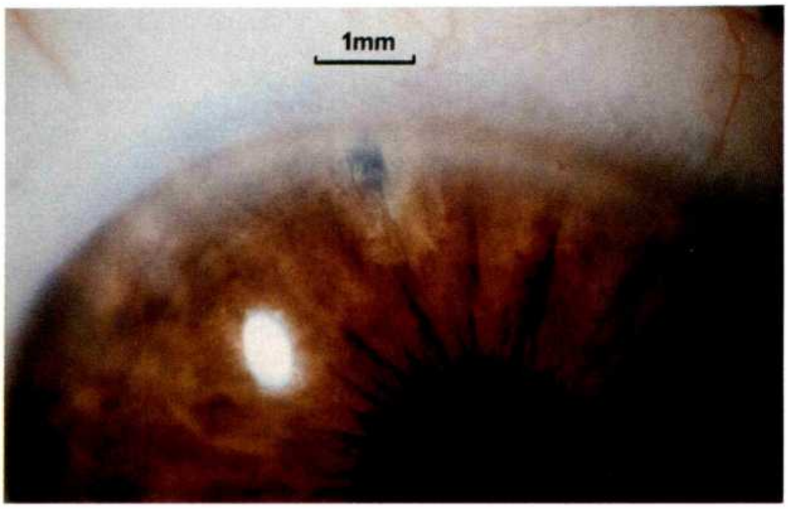


Figure 2 Case 2. Following laser enlargement all symptoms resolved and provocation testing was negative. Iridotomy diameter 200 μm.

CASE 3

An 83-year-old woman presented with intermittent pain in the left eye. The intraocular pressure was 44 mmHg, the anterior chamber was deep, and Goldmann gonioscopy revealed 90° of angle closure superotemporally. The plane of the iris was flat, with an anteriorly placed iris insertion. The right eye had a similar angle configuration, with normal intraocular pressure. Plateau iris configuration was diagnosed. Intraocular pressure in the left eye quickly returned to normal after treatment with acetazolamide 500 mg orally and pilocarpine eyedrops 2% hourly. Gonioscopy revealed 180° of angle closure superiorly. Nd-YAG laser iridotomy was performed three days later. The iris was light grey, with no crypts. A treatment site 1 mm from the limbus at 2 o'clock was selected. Four 10·9 mJ pulses produced a moderately large (200×400 μm) patent iridotomy. There was minimal iris bleeding at the time of treatment.

After this treatment, eyedrops of Timolol 0·5% twice daily, cyclopentolate 1% twice daily, and betamethasone 0·1% four hourly were prescribed. Fourteen days later the patient returned with pain and reduced vision of 24 hours' duration in the left eye. The intraocular pressure was 50 mmHg. After treatment with Pilocarpine eyedrops 2% and timolol eyedrops 0·5% the intraocular pressure fell to 7 mmHg. The iridotomy was patent and moderately large (200×400 μm). Identation gonioscopy revealed goniosynechiae over 150° superiorly, with plateau iris configuration. A sector iridectomy was performed. On further follow-up the intraocular pressure in the left eye was found to be 28 mmHg on no treatment, falling to 21 mmHg on addition of timolol eyedrops 0·5% twice daily. Gonioscopy revealed an open angle throughout 360°.

CASE 4

A 71-year-old hypermetropic woman presented with left acute angle closure glaucoma of eight hours' duration. The intraocular pressure was 46 mmHg and the anterior chamber was shallow. The right eye had a normal intraocular pressure and a shallow anterior chamber. After medical treatment with acetazolamide 500 mg intravenously and pilocarpine eyedrops 2% hourly the left intraocular pressure fell to 9 mmHg within two hours. Goldmann gonioscopy revealed 150° of angle closure superiorly. The right eye also had a very narrow angle, with 150° of angle closure superiorly.

Nd-YAG laser iridotomy was attempted in the left eye the next day. The iris was brown, with no crypts. Three 9·9 mJ pulses were delivered to two sites, with no penetration. Three days later four 10·2 mJ pulses were delivered, two to each of the previous treatment sites. The final pulse produced a very small, patent iridotomy at 2 o'clock, in the mid iris position. A single enlarging pulse of 9·2 mJ was delivered to this site on the following day. A very small (50 μm) iridotomy resulted. The patient was discharged home with betamethasone eyedrops 0·1% twice daily and cyclopentolate eyedrops 1% once daily to the left eye.

She returned six days later complaining of severe pain in the left eye. The intraocular pressure was 45 mmHg, and the anterior chamber was very shallow. The iridotomy was patent but very small. The intraocular pressure quickly fell to 8 mmHg after treatment with acetazolamide 500 mg intravenously and pilocarpine eyedrops 2% hourly. A surgical peripheral iridectomy was performed the next day.

Postoperatively the patient was treated with betamethasone eyedrops 0·1% four times daily and tropicamide eyedrops 1% once daily. Two days later she complained of pain over the left eye. The pupil was dilated, and the peripheral iridectomy was patent. The intraocular pressure was 41 mmHg. Gonioscopy was not tolerated. The intraocular pressure fell to 10 mmHg after treatment with acetazolamide 250 mg orally twice daily, pilocarpine eyedrops 2% four times daily, and timolol eyedrops 0·5% twice daily. Long term treatment with pilocarpine eyedrops 2% four hourly and timolol eyedrops 0·5% twice daily has been necessary to maintain normal intraocular pressure in the left eye.

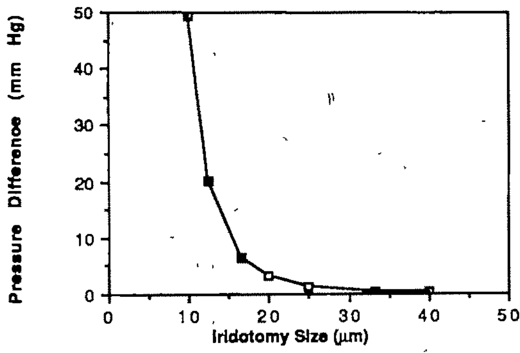


Figure 3 Pressure difference across the iris as a function of iridotomy size.

MATHEMATICAL MODEL

A very small iridotomy may be of inadequate physical size to by-pass pupil block adequately. Given a constant rate of aqueous flow, the pressure difference across an iridotomy increases as the size of the iridotomy decreases. Increased posterior chamber pressure relative to anterior chamber pressure will result in iris bombé. The degree of bombé is dependent on the rigidity of the iris and the pressure difference across the iris. At a critical level, dependent on peripheral anterior chamber depth, iris bombé may become sufficient to cause iridocorneal contact over a large enough extent of the angle to precipitate acute angle closure glaucoma.[16,17,19,20]

The minimum 'safe' size of an iridotomy may be calculated from a simple mathematical model. Firstly, an assessment is made as to whether aqueous flow is laminar or turbulent through an iridotomy aperture of 10 μm. On the assumption that aqueous viscosity equals the viscosity of water ($\eta = 10^{-3}$ Newton seconds per square metre), aqueous density equals the density of water ($\varrho = 1000$ kilograms per cubic metre), and aqueous flow, Q, is approximately 2 μl per minute ($3{\cdot}3 \times 10^{-11}$ cubic metres per second), as measured by Bloom *et al*,[21] then Reynolds' number for the system may be calculated.

If the iridotomy size (d) is 10 μm diameter, the aqueous velocity

$$v = \text{flow}/\pi r^2 = 4{\cdot}2 \times 10^{-1}\ \text{ms}^{-1}.$$

Reynolds' number for the system

$$R = \varrho v d/\eta,\ R = 42.$$

If R is considerably less than 1000, flow is laminar. Aqueous flow through an iridotomy of diameter 10 μm or larger will be laminar.

Secondly, the iridotomy channel may be considered to be a pipe of length 50 μm on the assumption that the peripheral iris thickness is 50 μm. The pressure drop (pd) along a pipe of length l=50 μm, diameter d=100 μm, at flow rate Q is expressed by the formula:

$$\begin{aligned} pd &= 128\eta l Q/\pi d^4 \\ &= 128 \times 10^{-3} \times 5 \times 10^{-5} \times 3{\cdot}3 \times 10^{-11}/3{\cdot}142 \times 10^{-16} \\ &= 0{\cdot}672\ \text{Nm}^{-2} \\ &= 0{\cdot}00494\ \text{mmHg, as } 1\ \text{mmHg} = 136\ \text{Nm}^{-2}. \end{aligned}$$

An iridotomy of 100 μm diameter will have a pressure drop of 0·00494 mmHg across it on the assumption of total pupil block.

However, as pd is proportional to $1/d^4$, if the diameter of the iridotomy were 50 μm pd would be 0·079 mmHg, under the same conditions. If the iridotomy were 25 μm, the pd would be 1·27 mmHg. If the iridotomy were 12·5 μm, the pd would be 20·2 mmHg, and if the iridotomy were 10 μm the pd would be 49·4 mmHg. It is not difficult to conceive that a pressure difference of 10–20 mmHg across the iris could result in significant iris bombé, with iridocorneal contact and angle closure. Such a pressure difference could develop if the size of the iridotomy was between 10 and 15 μm in diameter (Fig 3).

Discussion

Curran observed in 1920 that in some patients with glaucoma the passage of aqueous through the pupil appeared to be impeded by the iris 'hugging the lens over too great a surface extent'.[2] Surgical iridotomy allowed free drainage of fluid from the posterior chamber to the anterior chamber, with posterior movement of the iris and a reduction in intraocular pressure. Barkan elaborated the concept of pupil block as the causative mechanism of iris bombé, with resulting angle closure.[22] A peripheral iridectomy causes 'collapse' of iris bombé, resulting in widening of the 'entrance' to the angle.[22] Peripheral anterior chamber depth, but not central anterior chamber depth, increases following peripheral iridectomy[17,23,24] owing to resolution of iris bombé.

Failure of surgical peripheral iridectomy, or laser iridotomy, as evidenced by development of acute angle closure glaucoma, may occur by one of two mechanisms. A small number of cases of angle closure glaucoma are related to 'plateau iris configuration' – an anteriorly placed iris root, flat iris plane, and a normal or near normal anterior chamber depth. Pupil dilatation results in peripheral iris bunching, with occlusion of the trabecular meshwork.[13,25] As pupil block is not causative, surgical peripheral iridectomy or laser iridotomy are relatively ineffective in preventing further attacks of acute angle closure glaucoma. One of our patients (case 3) probably had plateau iris syndrome, and developed acute angle closure glaucoma following mydriasis despite the presence of a relatively large, patent iridotomy.

Case 4 developed acute angle closure glaucoma following mydriasis despite the presence of a small patent iridotomy and subsequently a larger surgical iridectomy. The mechanism of acute intraocular pressure rise may have been iris crowding in the angle. Plateau iris configuration was not present. Perhaps the term 'angle crowding' angle closure glaucoma would be a more appropriate term to use for eyes which develop acute angle closure glaucoma following mydriasis in the presence of a patent peripheral iridectomy. The cases of two other patients with moderately large peripheral iridectomies who developed acute angle closure glaucoma while using mydriatic drops have been reported.[14,15]

Mydriatic or dark room provocation tests following peripheral iridectomy have been found to be positive in 3–19% of cases.[25–28] Gonioscopy at the end of a positive test in eyes with patent peripheral iridectomies has revealed angle closure in some cases, due to angle crowding.[25,29] However, in other eyes the angle has been open.[25–27] Raised intraocular pressure in these eyes may be explained by the outflow facility lowering effect of anticholinergic drugs.[30] Surgical peripheral iridectomy appears entirely to overcome pupil block. No cases of acute angle closure glaucoma due to iris bombé have been reported in the presence of a patent surgical iridectomy.

Mydriatic provocation tests following argon laser iridotomy[31,32] and Nd-YAG laser iridotomy[33] have given similar results to those performed following surgical peripheral iridectomy. However, pilocarpine/phenylephrine tests have been negative in all eyes tested following argon laser iridotomy[34] or Nd-YAG laser iridotomy.[8,12] The test produces only moderate mydriasis, and increased tone in both the sphincter and dilator muscles of the iris may prevent angle crowding. The test induces maximal pupil block,[35] and failure to obtain any positive results suggests that pupil block was fully overcome in all cases tested.

Acute angle closure glaucoma in the presence of a small, patent argon laser iridotomy has previously been reported in two patients.[9,10] Mandelkorn *et al* reported a case of acute angle closure glaucoma following a 50 μm diameter argon laser iridotomy.[9] Further argon laser treatment was applied to the site, resulting in satisfactory long term pressure control. Brainard reported a similar case, in an eye with a 75 μm diameter argon laser iridotomy.[10] Further argon laser treatment to enlarge the iridotomy to 125 μm resulted in satisfactory long term intraocular pressure control, suggesting inadequate iridotomy size was responsible for initial failure.

Acute angle closure glaucoma has also been reported in the presence of a small, but patent Nd-YAG laser iridotomy.[11,12,33] Brazier reported two cases. One was treated by surgical peripheral iridectomy, with no further complications. The second was treated with miotics.[11] Wishart and Hitchings reported two cases of acute angle closure glaucoma and two cases of subacute angle closure glaucoma in the presence of patent Nd-YAG laser iridotomies.[33] In three cases the iridotomy was 100 μm diameter and in the fourth 150 μm. Gray *et al* reported two cases of acute angle closure glaucoma in the presence of a small, patent iridotomy.[12] One developed acute angle closure glaucoma while using pilocarpine eye drops 4%, and was treated by trabeculectomy. The second was treated by a further iridotomy. Intraocular pressure subsequently remained normal in both cases. Two of our cases (cases 1 and 2) behaved in a very similar way to the two cases reported by Gray *et al.* Case 1 responded to trabeculectomy, and case 2 responded to laser enlgargement of the iridotomy. The occurrence of acute angle closure glaucoma in the presence of a small, but patent, iridotomy which responds to surgical peripheral iridectomy or laser enlargement, suggests the size of the initial iridotomy was inadequate.

Wishart studied iris bombé using slit-lamp photographic assessment of peripheral anterior chamber depth. In four eyes with very small iridotomies and progressive narrowing of the angle, repeat laser iridotomy resulted in deepening of the peripheral anterior chamber.[33] This study provides further evidence that very small iridotomies may not fully relieve iris bombé.

We have calculated that the minimum functional iridotomy size should be approximately 15 µm, as previously suggested by Wheeler.[36] However, our clinical experience, and that of others,[9-12,33] shows that iridotomies in the range of 50–150 µm diameter may fail to prevent acute angle closure glaucoma.

Several factors may contribute to the reduction in size of an iridotomy of theoretically 'safe' size below that needed to prevent acute angle closure glaucoma. Most cases of acute angle closure glaucoma following Nd-YAG laser iridotomy have occurred within one month of treatment. Naveh *et al* observed rapid diminution of Nd-YAG laser iridotomy size within an hour of treatment in six eyes.[37] In each case a return to original treatment size occurred within two weeks. Localised iris oedema round the treatment site could be responsible.

Re-closure of Nd-YAG laser iridotomies due to iris pigment epithelium proliferation is unusual, and tends to occur 1–4 months after treatment.[11 12 33 37 38] Re-closure resulted in acute angle closure glaucoma in two eyes reported on by Wishart and Hitchings[33] and one eye reported on by Gray *et al.*[12]

Case 2 developed acute angle closure glaucoma following mydriasis. Pupil dilatation might reduce the surface area of some iridotomies, and folds of iris tissue might functionally block an iridotomy when the pupil is dilated. Mydriatics might therefore produce acute angle closure glaucoma in the presence of a patent iridotomy by two mechanisms – pupil block due to reduction of iridotomy size, and angle crowding.

To answer the question, How large must an iridotomy be to prevent acute angle closure glaucoma? several factors must be considered. In forms of angle crowding angle closure glaucoma, such as plateau iris syndrome, a large iridotomy will not prevent the development of acute angle closure glaucoma following mydriasis, as pupil block is not causative.

Theoretical modelling suggests an iridotomy of 10–15 µm diameter will prevent angle closure glaucoma due to pupil block. However, an iridotomy of greater size may fall below this critical level due to early post-treatment oedema, late pigment epithelium proliferation, or pupil dilatation. Wishart and Hitchings reported subacute angle closure glaucoma in an eye with a 150 µm diameter iridotomy.[33] All other cases of acute angle closure glaucoma in the presence of a patent iridotomy have occurred in eyes with an iridotomy of less than 100 µm in diameter. The smallest potentially safe size of an iridotomy would therefore appear to be 100 µm. However, in order to incorporate a safety margin, we would recommend that iridotomies should be at least 150–200 µm in diameter.

Provocation tests have not been helpful in identifying eyes at risk, as eyes developing acute angle closure glaucoma following Nd-YAG laser iridotomy have done so before a provocation test had been performed.[8 12 33] If provocation tests are to be employed, we suggest the use of tropicamide eyedrops 1% soon after the iridotomy has been performed, in order to detect cases at risk of developing acute angle closure glaucoma. Routine pupil dilatation to prevent posterior synechiae formation following laser iridotomy may be more safely achieved with phenylephrine eyedrops 10%, with measurement of intraocular pressure following dilatation. Lowe has shown that phenylephrine very rarely results in a rise in intraocular pressure following peripheral iridectomy,[15] and the effect may be quickly reversed using thymoxamine eyedrops 0·5% if a pressure rise does occur.

Dr N A Fleck, Department of Engineering, University of Cambridge, developed the mathematical model Professor C I Phillips and Dr J F Cullen, Department of Ophthalmology, Edinburgh Royal Infirmary, made helpful comments during preparation of the manuscript. Mr Stuart Gairns, ophthalmic photographer, assisted in preparation of the illustrations

This paper forms part of an ongoing research programme funded by the W H Ross Foundation.

1 Von Graefe A. Uber die Iridectomie bei Glaucoma und uber den glaucomatosen Process. *Graefes Arch Clin Exp Ophthalmol* 1857; 3: 456–555
2 Curran EJ. A new operation for glaucoma involving a new principle in the aetiology and treatment of chronic primary glaucoma *Arch Ophthalmol* 1920; 49: 131–55.
3 Curran EJ Peripheral iridotomy in acute and chronic glaucoma: some results after 10 years duration. Anatomical classification of glaucoma. *Trans Ophthalmol Soc UK* 1931, 51: 520–38.
4 Gifford H. Peripheral iridotomy (Curran) in the treatment of glaucoma. *Am J Ophthalmol* 1921; 4: 889–94.
5 Chandler PA. Narrow angle glaucoma *Arch Ophthalmol* 1952, 47: 695–716.
6 Abraham RK, Miller GL Outpatient argon laser iridectomy for angle closure glaucoma: a two year study. *Ophthalmology* 1975; 79: OP529–38.
7 Frankhauser F, Roussel P, Steffen J, Van Der Zyphen E, Chrenkova A. Clinical studies on the efficiency of high power laser radiation upon some structures of the anterior segment of the eye. First experience of the treatment of some pathological conditions of the anterior segment of the human eye by means of a Q-switched laser system *Int Ophthalmol* 1981; 3: 129–39.
8 Fleck BW, Fairley A, McGlynn C. A prospective comparison of Nd:YAG laser iridotomy and surgical peripheral iridectomy in the treatment of acute angle closure glaucoma *Proceedings of the XXVI International Congress of Ophthalmology*. Singapore (in press).
9 Mandelkorn R, Mendelsohn A, Olander K, *et al* Short exposure times in argon laser iridotomy *Ophthalmic Surg* 1981, 12: 805–9
10 Brainard JO, Landers JH, Shock JP Recurrent angle closure glaucoma following a patent 75-micron laser iridotomy a case report *Ophthalmic Surg* 1982; 13: 1030–2
11 Brazier DJ. Neodymium-YAG laser iridotomy *J R Soc Med* 1989; 79: 658–60.
12 Gray RH, Hoare Nairn J, Ayliffe WHR. Efficacy of Nd-YAG laser iridotomies in acute angle-closure glaucoma *Br J Ophthalmol* 1989; 73: 182–5
13 Wand M, Grant WM, Simmons RJ, Hutchinson BT Plateau iris syndrome. *Ophthalmology* 1977; 83: 122–30.
14 Douglas WHG, Strachan IM Surgical safety of prophylactic peripheral iridectomy. *Br J Ophthalmol* 1967; 51: 459–62.
15 Lowe RF. Primary angle-closure glaucoma postoperative acute glaucoma after phenylephedrine eyedrops. *Am J Ophthalmol* 1968; 65: 552–4.
16 Phillips CI. Sectorial distribution of goniosynechiae. *Br J Ophthalmol* 1956; 40: 129–35.
17 Phillips CI. Closed-angle glaucoma. Significance of sectorial variations in angle depth *Br J Ophthalmol* 1956, 40: 136–43
18 Mapstone R. Provocative tests in closed-angle glaucoma. *Br J Ophthalmol* 1976; 60: 115–9
19 Bhargava SK, Leighton DA, Philips CI. Early angle-closure glaucoma. Distribution of iridotrabecular contact and response to pilocarpine. *Arch Ophthalmol* 1973; 89: 369–72.
20 Mapstone R. One gonioscopic fallacy *Br J Ophthalmol* 1979; 63: 221–4.
21 Bloom JN, Levene RZ, Thomas G, Kimura R Fluorophotometry and the rate of aqueous flow in man. *Arch Ophthalmol* 1976; 94: 435–43.
22 Barkan O. Iridectomy in narrow angle glaucoma *Am J Ophthalmol* 1954; 37: 504–19.
23 Jacobs IH, Krohn DL. Central anterior chamber depth after laser iridectomy. *Am J Ophthalmol* 1980; 89: 865–7
24 Lee DA, Brubaker RF, Ilstrup DM Anterior chamber dimensions in patients with narrow angles and angle-closure glaucoma *Arch Ophthalmol* 1984; 102: 46–50
25 Lowe RF. Primary angle closure glaucoma – investigations after surgery for pupil block. *Am J Ophthalmol* 1964, 57: 931–8.
26 Harris LS, Galin MA. Cycloplegic provocative testing. *Arch Ophthalmol* 1969; 81: 356–8.

27 Friedman Z, Neumann E. Comparison of prone position, dark room, and mydriatic tests for angle closure glaucoma before and after peripheral iridectomy *Am J Ophthalmol* 1972; **74**: 24–7

28 Hung PT, Chou LH. Provocation and mechanism of angle-closure glaucoma after iridectomy *Arch Ophthalmol* 1979; **97**: 1862–4.

29 Godel V, Stein R, Feiler-Ofrey V Angle-closure glaucoma following peripheral iridectomy and mydriasis. *Am J Ophthalmol* 1968; **65**: 555–60.

30 Harris LS. Cycloplegic induced intraocular pressure elevations *Arch Ophthalmol* 1968; **79**: 242–6.

31 Karmon G Vender T, Savir H. Evaluation of laser iridectomy in angle-closure glaucoma· provocative tests. *Br J Ophthalmol* 1982; **66**: 471–3.

32 Yassur Y, Melamed S, Cohen S, Ben-Sira I Laser iridotomy in closed angle glaucoma *Arch Ophthalmol* 1979, **97**: 1920–1.

33 Wishart PK, Hitchings RA. Neodymium YAG and dye laser iridotomy – a comparative study. *Trans Ophthalmol Soc UK* 1986; **105**: 521–40.

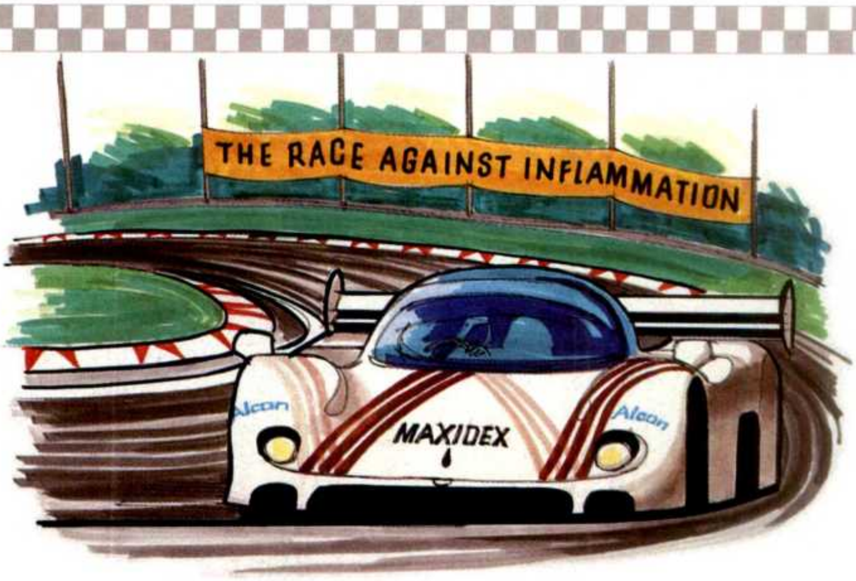
34 Harrad RA, Stannard KP, Shilling JS. Argon Laser iridotomy *Br J Ophthalmol* 1985; **69**: 368–72.

35 Mapstone R. Mechanics of pupil block. *Br J Ophthalmol* 1968; **52**: 19–25.

36 Wheeler CB: Laser iridectomy. *Phys Med Biol* 1977; **6**: 1115–35.

37 Naveh N, Zborowsky-Gutman L, Blumenthal M. Neodymium-YAG laser iridotomy in angle closure glaucoma: preliminary study. *Br J Ophthalmol* 1987, **71**: 257–61

38 McAllister JA, Schwartz LW, Moster M, Spaeth GL. Laser peripheral iridectomy comparing Q-switched neodymium YAG with argon. *Trans Ophthalmol Soc UK* 1985; **104**: 67–9.



FAST THROUGH CORNEAS.

Maxidex ophthalmic suspension has proven to be a fast and effective treatment for intraocular inflammation.

Fast, because human studies[1] show that levels of dexamethasone were detectable in aqueous humour 20 minutes after topical administration of Maxidex — demonstrating rapid penetration of the human cornea.

Effective, because in the same studies peak levels of dexamethasone were achieved in human aqueous between 91 and 120 minutes after instillation of Maxidex.

Furthermore, 75% of peak concentration is still present after 4 hours, thus maintaining adequate levels between doses.

For full information contact Alcon Laboratories.

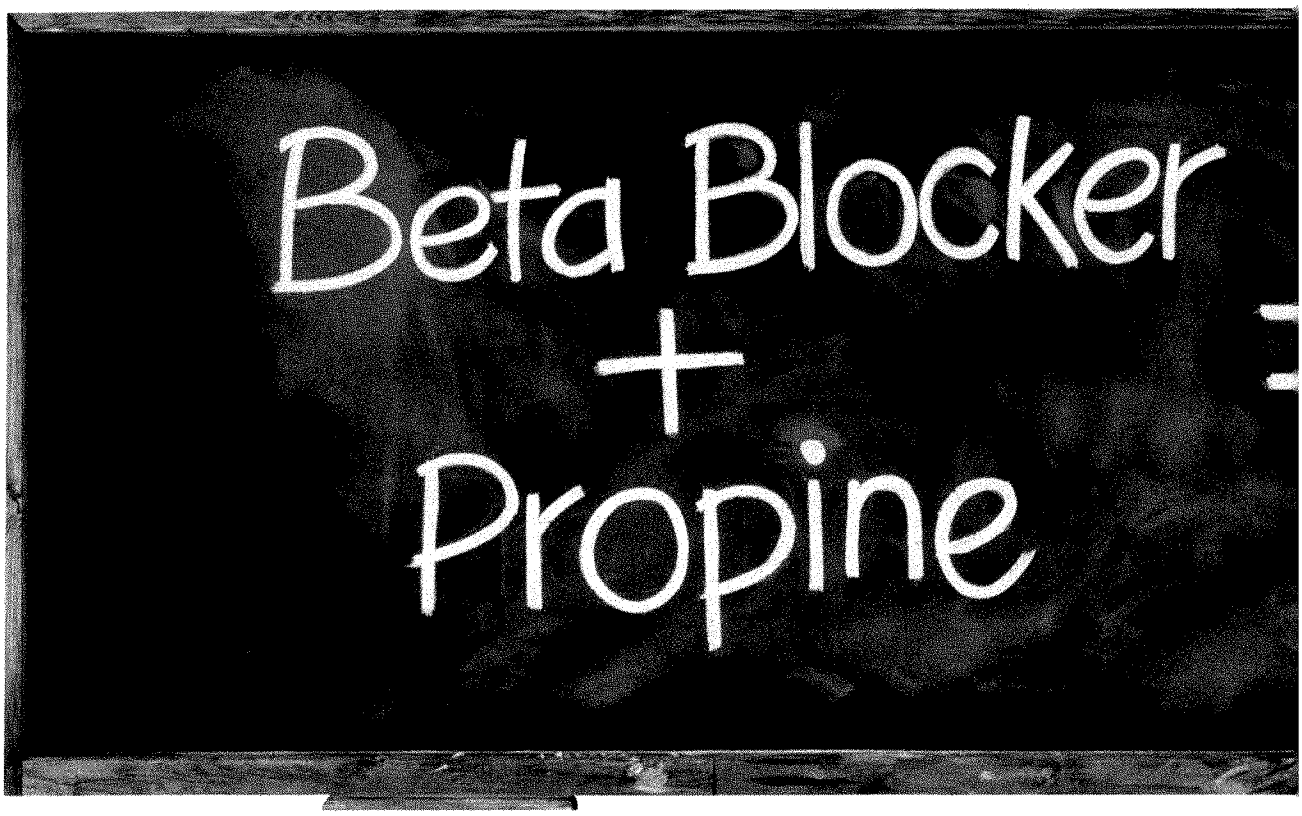
MAXIDEX
Dexamethasone
Ph. Eur. 0.1%
FAST & EFFECTIVE

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford, Herts. WD2 4YR
Tel (0923) 246133 Fax (0923) 243331

REFERENCE: 1. Watson, D. et al.: Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humor, Arch Ophthalmol 106: 686 687, 1988.

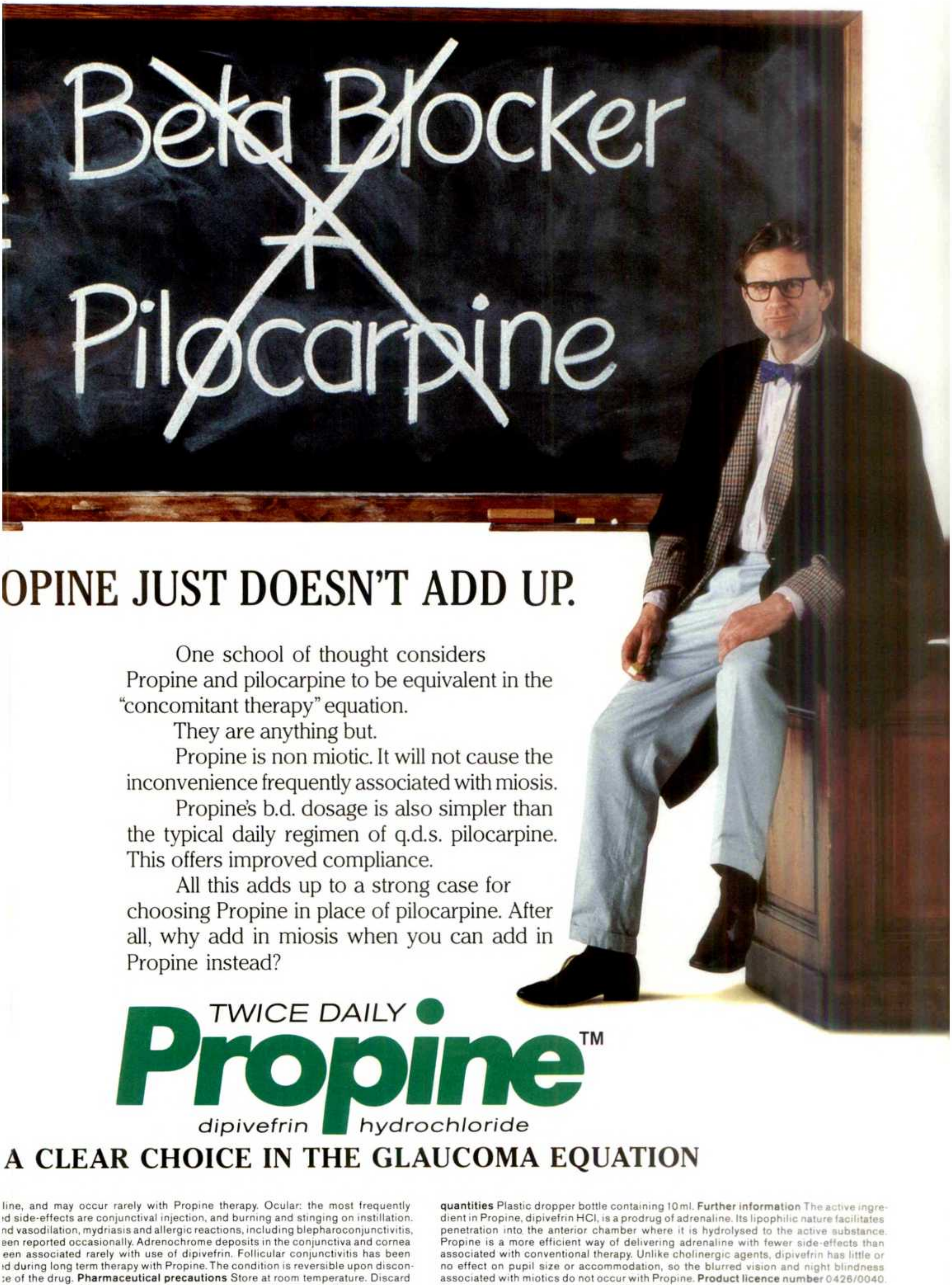
PRODUCT INFORMATION: Presentation: Dexamethasone PhEur 0.1% in a sterile, isotonic, ophthalmic suspension preserved with Benzalkonium Chloride BP 0.01%. **Uses:** Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and administration:** One or two drops topically in the conjunctival sac(s) four to six times daily. In severe disease, drops may be used hourly. **Contra-indications:** Epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; tuberculosis of the eye; and in those persons who have shown hypersensitivity to any component of this preparation. **Warnings:** Use in the treatment of herpes simplex requires great caution. Not effective in the treatment of Sjorgen's keratoconjunctivitis. Infection appears to be enhanced with the presence of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. It is advisable that the intraocular pressure be checked frequently. This product contains benzalkonium chloride and should not be used when soft contact lenses are being worn. **Adverse reactions:** Glaucoma with optic nerve damage, visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe may occur. **Pregnancy warning:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long-term treatment of pregnant patients. **Legal category:** POM. **Package quantities:** 5 ml and 10 ml. **P.L.:** 0649/5914.



EQUATING PILOCARPINE WI

PROPINE™ Prescribing Information

Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be
with caution in patients with narrow angles since dilation of the pupil may trigg
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrer
use in aphakic patients. Prompt reversal generally follows discontinuance of the
Macular oedema with dipivefrin does present as a possibility in the aphakic patient
product contains benzalkonium chloride and should not be used by patients conti
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachyc
arrhythmias and hypertension have been reported with ocular administratic



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

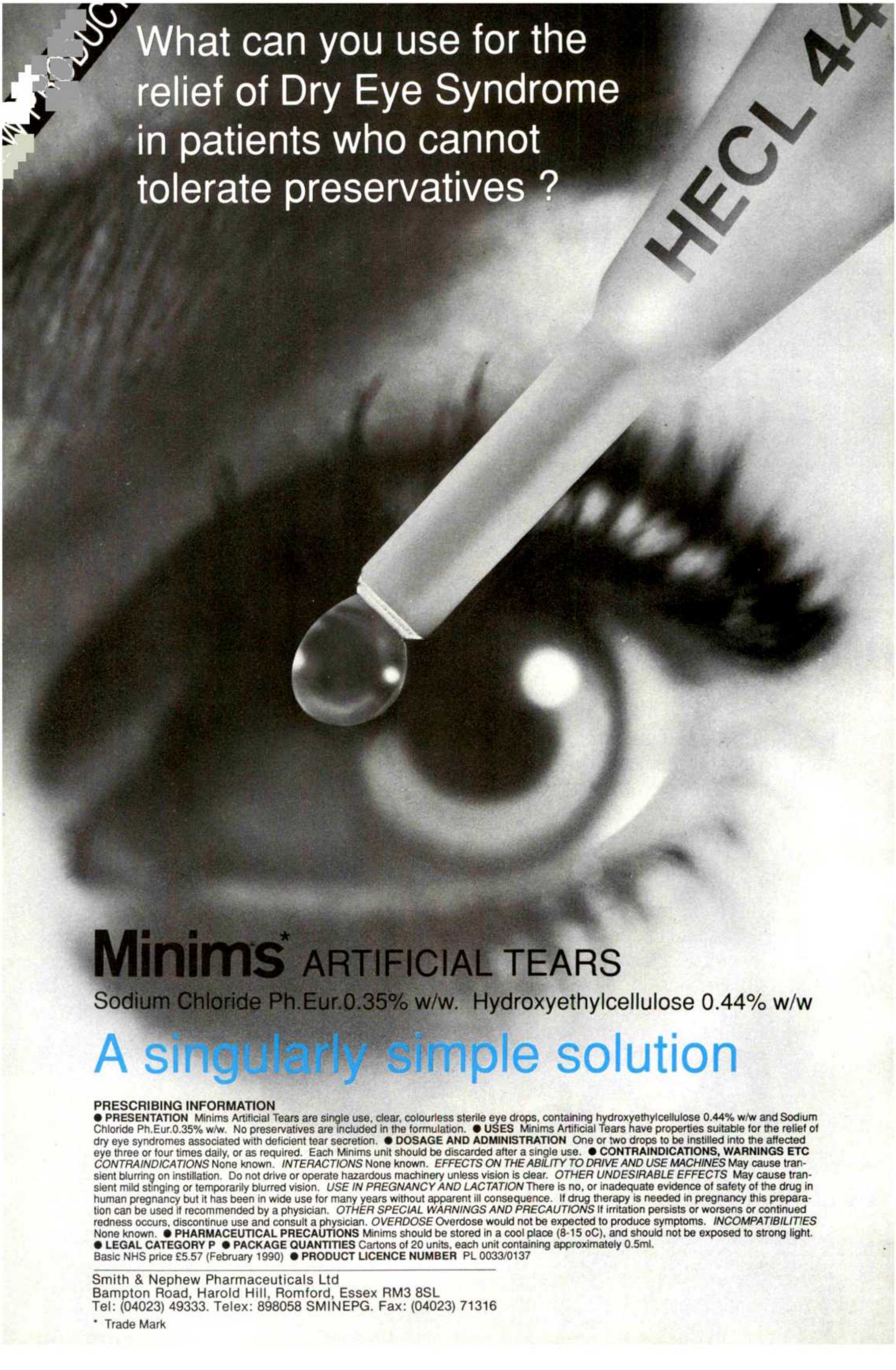
All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY
Propine™
dipivefrin hydrochloride

A CLEAR CHOICE IN THE GLAUCOMA EQUATION

line, and may occur rarely with Propine therapy. Ocular: the most frequently d side-effects are conjunctival injection, and burning and stinging on instillation. nd vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis, een reported occasionally. Adrenochrome deposits in the conjunctiva and cornea een associated rarely with use of dipivefrin. Follicular conjunctivitis has been d during long term therapy with Propine. The condition is reversible upon discon- e of the drug. **Pharmaceutical precautions** Store at room temperature. Discard used contents 28 days after opening the bottle. **Legal category** POM. **Package quantities** Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990.

TM denotes trademark ALLERGAN PHARMACEUTICALS



What can you use for the relief of Dry Eye Syndrome in patients who cannot tolerate preservatives ?

Minims* ARTIFICIAL TEARS

Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

A singularly simple solution

PRESCRIBING INFORMATION

● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml.
Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

* Trade Mark

British Journal of Ophthalmology, 1990, 74, 589–594

A longitudinal study of children with a family history of strabismus: factors determining the incidence of strabismus

E Aurell, K Norrsell

Abstract

A longitudinal study of ocular refraction, position, and fixation was performed in children with a family history of strabismus. The children were examined at regular intervals between 3 months and 4 years of age, and the results are discussed in terms of changes in refraction between different ages and correlations between refraction and development of strabismus and amblyopia. Six of 34 children (17·6%) developed constant or intermittent esotropia. The strabismus was first noted between 18 and 30 months of age except in one case. All esotropic children were 4 dioptres hypermetropic or more at 6 months, and their hypermetropia remained almost unchanged through the years. Seven additional children were 4 dioptres or more hypermetropic at 6 months but did not develop a squint. In contrast to the squinting children the hypermetropia in these children changed towards emmetropia. This emmetropisation was most pronounced during the first 2 years of age. The implications of these results for an early diagnosis of strabismic amblyopia are discussed.

One main reason for examining the eyes of preschool children is to detect errors which might cause amblyopia. The simplest method is monocular testing of vision but this is difficult in small children. We doubt whether it could be performed before the age of 4 as a population screening method, since it requires trained staff and even so would probably not be reliable for all children. In Sweden all 4-year-old children have their vision screened at the Children's Health Care Centre, and those who present subnormal results are referred to an ophthalmologist for further evaluation. Köhler and Stigmar[1] have reported a study of 2447 4-year-old randomly selected children. Of these children 358 were referred to an ophthalmologist, and 12·3% in this group were considered amblyopic.

It is generally believed that amblyopia and disorders in binocular function should be detected and treated as early as possible, but there is no easy and reliable method of detecting these disorders in young children. Nor is it known how many people are actually suffering from visual problems which could have been prevented had they been detected earlier. If the assumption is made that amblyopia therapy should be started earlier than at present, then the question arises how to find the children at risk. Ingram[2] suggested that refraction should be the basis for screening young children. He argued that there was a close association between hypermetropia and the development of squint and/or amblyopia. He also found that amblyopia was highly likely if a child had a meridional hypermetropia of more than 3 dioptres at the age of 1 year.[3] In many of these children the amblyopia could not be corrected.

Before even contemplating a nationwide refraction screening of small children we must be more confident than we are today about what an individual refraction at a certain age means for the child's vision in the future. By relating his own observations to the reports of others Fabian[4] suggested that the refractions of small children develop towards emmetropia (emmetropisation). This theory is supported by Ingram and Barr,[5] but only if the refractions of individual meridians are considered. They found no decrease in hypermetropia between the ages of 1 and 3·5 years. Astigmatism decreased significantly, however, and anisometropia was unstable. Even if the number of anisometropic children was roughly the same at 1 as at 3·5 years, they were mostly different individuals. Similar reductions in astigmatism and instability in anisometropia between 1 and 4 years have been found by Abrahamsson *et al.*[6] Unstable refraction does not necessarily imply emmetropisation but instability as such creates difficulties in determining when glasses should be given. Medina[7] has proposed a mathematical model for the emmetropisation process. The model implies a feedback mechanism operating towards reducing the refractive error, and Medina concludes that corrective lenses influence this process.

Our knowledge of the normal development of ocular refraction is still fragmentary because longitudinal studies are few. It seems that we cannot, except in special cases, predict with certainty which children are going to develop amblyopia judging from the results of one single refraction at one particular age. More longitudinal studies of the development of refraction during infancy and in early childhood are needed before we can be absolutely certain when a prescription of glasses is due in a small child, especially when the testing of visual acuity is difficult. The practical problems with glasses and amblyopia therapy are seldom mentioned in the literature. Parents are concerned about their child's vision, and they usually try very hard to follow the instructions. We must be reasonably sure that their efforts are worthwhile.

We know, however, that some groups of children run a greater risk than others of developing strabismus and amblyopia. Heredity is one factor of importance in determining the risk,[8] though we do not know what factor is inherited nor what the mode of inheritance is. In

Department of Ophthalmology, County Hospital, Mölndal, Sweden
Elisabeth Aurell

University Eye Clinic, Sahlgren's Hospital, Göteborg, Sweden
Kerstin Norrsell

Correspondence to:
K Norrsell, MD,
University Eye Clinic,
Sahlgren's Hospital, S 413 45
Goteborg, Sweden.

Accepted for publication
19 April 1990

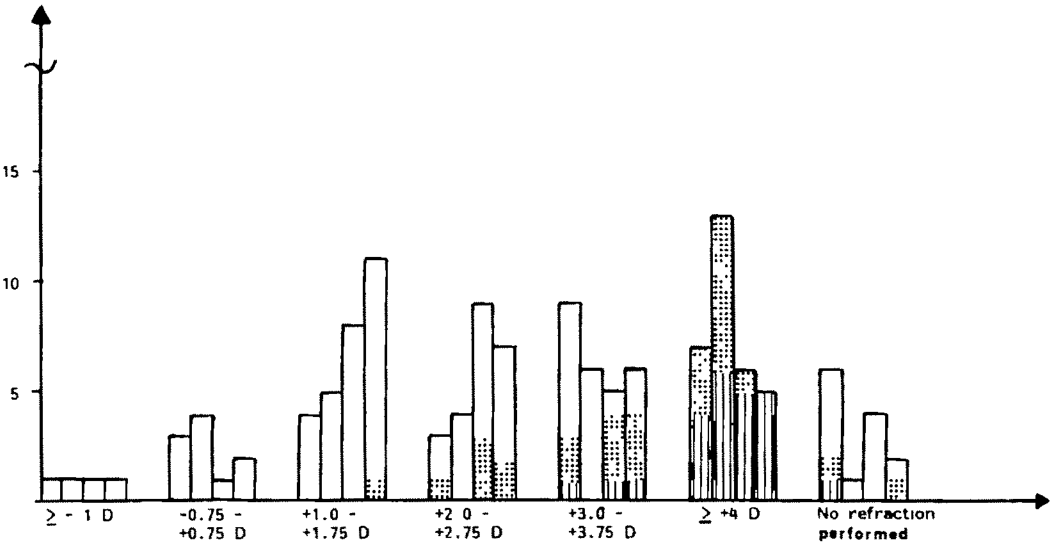


Figure 1 Refractions at four different ages for the whole material (34 children). On the x axis seven groups of columns with four columns in each group are shown. The groups except the one to the far right each represent a certain refraction span, indicated below the group. The single group to the right represents those who could not be examined at those particular ages. The four columns in each group represent from left to right 3 months, 6 months, 2 years, and 4 years of age. The y axis indicates the number of children in the different columns. The stripes and dots together represent the hypermetropic group, the stripes the eso group and the dots the non-eso group (see text for explanations). By definition the column representing +4 D or more at 6 months (the second column in the sixth group) consists of only stripes and dots, since the hypermetropic group is defined by being +4 D or more at 6 months At 4 years only the eso group is still +4 D or more.

this study we therefore chose heredity as the single determining factor in order to select newborn children for a longitudinal study of ocular refraction, position, and fixation.

Material and methods

The incidence of strabismus and the development of refraction were studied in a group of children with one common denominator: heredity for strabismus. The children were recruited from an average Swedish town and country population during a given time. All mothers who were delivered of a living child between 15 February and 30 June 1981 at the county hospital in Mölndal, Sweden, were asked if the newborn child's parents or siblings had or used to have a squint. The questions were asked by the paediatrician who examined the child immediately before mother and child left the ward. All mothers who had given Yes for an answer were contacted within one month by one of the authors. Additional questions were asked on the history of strabismus. Convergent strabismus was thus confirmed in parents and/or siblings of 39 children.

We did not attempt to find any records of their strabismus for two reasons. First, we had no intention of studying heredity as such; secondly, we wanted to see if an amblyopia risk group could be defined in a simple and clinically applicable way. We judged it impossible to find strabismus records for all parents after, in many cases, more than 20 years. All parents of the 39 children were willing to take part in the study with their child. During the time of the study (four years) five children were lost from it. Three moved to other parts of Sweden and could not be reached, one parent refused to let us give cyclopentolate, and one child did not turn up in spite of repeated calls. Thirty four children completed the whole study.

During the first visit the parents were informed about the purpose of the study. They were told to look for signs of strabismus and were instructed about what to look for. They were encouraged to call and report if they made any observations of interest. The children were

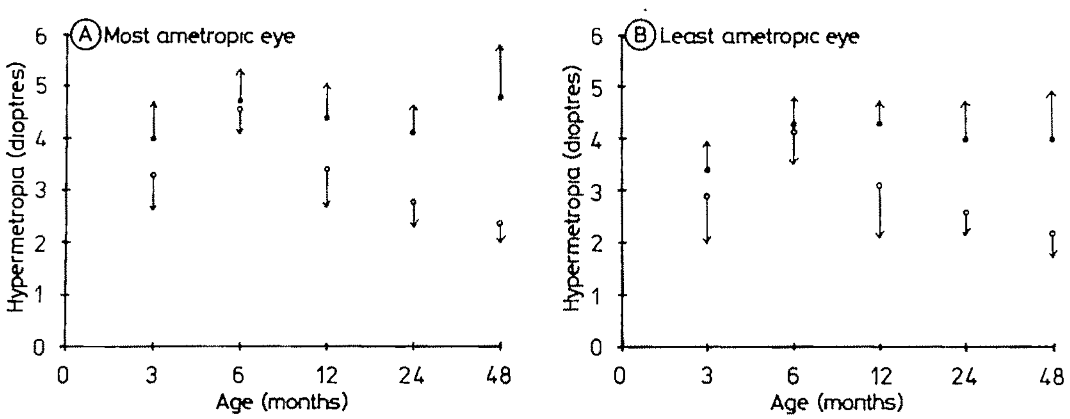


Figure 2 Mean and standard deviation for the refractions of the most ametropic meridian of the most (left) and the least (right) ametropic eye for the hypermetropic group. The eso group is represented by filled circles and the non-eso group by open circles.

Table 1 Refraction for the hypermetropic group at five different ages between 3 months and 4 years. The approximate age when strabismus was first noted, the presence of amblyopia therapy, and the visual acuity at 4 years are shown. Right eye always presented above left. The first six children constitute the eso group

Child no	*3 months*	*6 months*	*1 year*	*2 years*	*4 years*	*Start of squint*	*Amblyopia therapy*	*Visul acuity at 4 years*
1	+4·0 +4 0	+5·0–1 0 90° +5 0–1·0 90°	+5 0–2 0 90° +5·0–2 0 90°	+5·0–2 0 90° +5·0–2 0 90°	+5 0–2 0 90° +5 0–2·0 90°	2 yr	No	0 8 C 0 7
2	+3 0–1 0 90° +5·0	+4·0–0 5 140° +5 5–1 0 150°	+4·5 +4 5	+4 5 +5 0	+5·5 +6 5–0·5 90°	2·5 yr	Yes	0 4 C 0 5
3	+3·0 +3·0	+4·0 +4·0	—	+4 0 +4·0	+4 0–1 0 0° +5·0–1 0 0°	2 yr	Yes	0 5 C 0 1
4	—	+5 0–1·0 0° +5 0–2 0 0°	+4 0–2 0 0° +4·0–2·0 0°	+4·0–2 0 0° +4·0–1·0 0°	+5 0–1 0 0° +3 5	2 5 yr	Yes	0 4 C 0 6
5	+3 0 +4·0	+4·0–1 0 90° +5 0–1 0 90°	+4·0–1·0 90° +5·0–2 0 90°	+3 0–2·0 90° +4 0–2 0 90°	+3·0–2 0 90° +4 0–2 0 90°	1 5 yr	No	0 5 C 0 4
6	+4 0 +4·0	+4 0–1 0 0° +4 0	+3·5 +4·0	+3·0 +3·5	+3 0 +3·5	4 yr	No	0 7 UC 0 6
7	+5·0 +5 0	+5·0 +5·0	+4·5 +4·5	+3·0–0·5 90° +3 5–0·5 90°	—	—	No	1 0 UC 1 0
8	+3 0 +3 0	+4·5–1 0 90° +4 5–1 0 90°	—	+2 5 +2 5	+2 5–1·0 90° +2 5–1 0 90°	—	No	0 7 UC 0 7
9	—	+3·0–1 0 90° +4 0–2·0 90°	—	+4·0–2 0 90° +4·0–2 0 90°	+3 0–1 0 90° +3·0–1 0 90°	—	No	0 7 UC 0·7
10	+3 5–1 0 90° +4 0–1 5 90°	+4 0–1·0 90° +5·0–1 0 90°	—	+3·0–1 0 90° +3·5–1·5 90°	+3·0–1 0 90° +3·5–1·0 90°	—	No	0 7 UC 0 7
11	+2 0 +3·0	+4 0–2·0 90° +4 0	+3·0 +3 0	+2 5 +2 5	+1 0 +1 0	—	No	0 8 UC 0 7
12	+2·5 +2 0	+5 0 +4·0	+3 0 +4 0	+3·0 +3 0	+2 5–0 5 0° +2·0	—	No	0 7 UC 0 7
13	+4 0–0·5 0° +5·0–0 5 0°	+4·0–0·5 0° +4 0–0·5 0°	+3 5–0·5 0° +3·5–0·5 0°	+2·5–0·5 0° +2 5–0·5 0°	+2 0–0·5 0° +2 0	—	No	0 7 UC 0 7

C=corrected visual acuity. UC=uncorrected visual acuity

examined at 3, 6, 12, 18, and 24 months, and at 4 years. On all these occasions fixation, position, motility, and the ocular fundus were examined. At 3, 6, 12, and 24 months, and at 4 years a retinoscopy after repeated instillations of 1% cyclopentolate solution was performed. At four years the visual acuity was measured by means of linear Es. Those who developed strabismus were treated conventionally with glasses and if necessary with occlusion. All examinations were performed by the authors except in some rare cases when the child at 4 had moved to a distant part of Sweden. In those cases the child was examined by the local ophthalmologist. Some of the children have been followed up beyond the age of 4.

Results

DEVELOPMENT OF REFRACTION

In Figure 1 the refractions of the most ametropic meridian of the most ametropic eye are shown for the whole group. We have chosen to compare the results of the retinoscopy at 3 months, 6 months, 2 years, and 4 years of age. There were some children who either did not come or could not be examined properly on all these occasions. Especially at 1 year there were some children in whom we failed to achieve a reliable retinoscopy. We have therefore refrained from including the figures for refraction at 1 year old when making comparisons for the whole group. The largest ametropia was found at 6 months. In the majority of cases the hypermetropia was less at 3 months than at 6 (Fig 1, Fig 2, Table 1). Thirteen of the 34 children, more than ⅓ of the whole group were 4 dioptres hypermetropic or more at 6 months. These 13 children have been followed up beyond the age of 4 years, and this article will mainly deal with their development. In this text they will be referred to as the *hypermetropic* group.

During the length of the study the refraction changed towards emmetropia in the majority of the children. A detailed analysis of this change has been done only for the hypermetropic group. Seven children in this group showed a decrease of hypermetropia from 6 months to 4 years; they started to become emmetropic. Since those 7 children did not show any strabismus they are called the *non eso* group. The remaining 6 children in the hypermetropic group had no decrease of hypermetropia; they failed to become emmetropic. Since they all developed an esotropia they are called the *eso* group.

The greatest changes towards emmetropia occurred during the first two years. At 2 years only six children were 4 dioptres hypermetropic or more and at 4 years only five. These five children together with a sixth child to be described below (no. 6 on Table 1) constitute the eso group, since they all eventually had an esotropia. Child no. 6 belongs by definition to the hypermetropic group, since her refraction at 6 months was +4 (Table 1). At both 2 and 4 years her retinoscopic refraction was +3·5. The girl was very uncooperative, however, but because her mother had repeatedly and increasingly observed, from about 4 years, that the child's left eye squinted she got another appointment at about 4½ years of age. On that occasion the examination was easy; her refraction was +4, and a cover test showed an esophoria with slow restitution. Because she was thought to be on the verge of manifest esotropia she was given glasses. Because of her failure to become emmetropic, and, because of the observations made by her mother and us, we decided that she should belong to the eso group, though with some hesitation, since we had not observed a spontaneous strabismus.

Table 1 shows that the emmetropisation process for the non-eso group was most pronounced before 2 years, but in some individuals it continued and we do not yet know what happens after 4 years. We do not have complete data from one year. Nine of the 13 children in the hypermetropic group allowed a reliable retinoscopy to be performed at 1 year, and seven of these were 4 dioptres hypermetropic or more. Five out of these seven belonged to the group who remained hypermetropic at 4 (the eso group). One child in the eso group could not be examined. Three children in the non-eso group could not be examined at 1 year. The remaining four were still hypermetropic (+3 to +4·5), but the emmetropisation process had started (Table 1).

Astigmatism was common in both the eso and the non-eso group as well as in the whole group. No obvious correlation between astigmatism and strabismus/amblyopia has been found. Anisometropia with a difference of about 1 dioptre was common. No obvious correlations can be drawn between anisometropia and strabismus/amblyopia, but it must be pointed out that we can neither confirm nor deny any importance of anisometropia in this context. All children in the eso group who required amblyopia therapy were anisometropic, but so were others. The material is too small for any conclusions to be drawn in this respect.

DEVELOPMENT OF STRABISMUS

One finding is obvious from these results regarding the development of refraction: children with a hypermetropia of 4 dioptres or more at 6 months either stayed hypermetropic at about the same degree throughout the investigation or started to become emmetropic. All those who stayed hypermetropic developed a convergent squint, the eso group. None of those who became emmetropic developed a squint, the non-eso group. Five started to squint between 1·5 and 2·5 years. Three of them required amblyopia therapy, two stayed straight after they got glasses. One (the above mentioned no. 6) was observed by her mother to squint before 4 years. An esophoria was observed by us at about 4½. The reasons for including this girl in the eso group have been explained above.

VISUAL ACUITY

Visual acuity was tested with linear Es at 4 years. All children were able to attend. We have defined amblyopia as an acuity difference between the eyes of more than one line. Three children had been put on amblyopia therapy (nos. 2, 3, and 4) a short time after the strabismus had been detected. Only one, no. 3, had at 4 a deep amblyopia which had resisted all treatment. No. 4 must also be considered as amblyopic, though not to the same extent. She was still wearing occlusion intermittently as well as no. 2. On the whole the visual acuity was lower bilaterally at 4 in the eso group than in the non-eso group. All children in the non-eso group as well as the remaining 21 children had at 4 a visual acuity of 0·7 or better and no bigger difference than one line between the eyes.

Discussion

The incidence of strabismus in a Caucasian population is generally considered to be 3–4%.[8] The risk for developing strabismus increases about four times if either of the parents have a squint.[9] Our results correspond well to this figure, since six children of 34 (17·6%) developed a convergent strabismus, constant or intermittent. All these children were hypermetropic. Three of the esotropic children required amblyopia therapy. Ingram *et al*[3] found that uncorrectable amblyopia was likely if a child had +3·5 or more dioptres of meridional hypermetropia at the age of 1 year. At one year only 26/34 could be reliably examined. Ten of these were +3·5 dioptres or more. Since only one child in the whole group had a deep amblyopia at 4 years, we doubt whether uncorrectable amblyopia would be likely. Since the end result of the amblyopia therapy is not complete at 4, we must postpone a definite statement.

We started this investigation on the assumption that an inheritance for strabismus increases the risk of developing strabismus, and the high percentage of esotropes confirms this assumption. One aim was to examine what other factors are of importance. As might be expected, we found that hypermetropia is important for strabismus. The exceptional observation in this study is that all those who started to squint had roughly the same hypermetropia at 4 years as at 6 months, the so called eso group. Children with the same amount of hypermetropia at 6 months as the eso group but who later decreased in their hypermetropia did not develop a squint, the non-eso group. One conclusion from these observations is that one should probably think twice before prescribing glasses to very small children. But what is the reason for these differences?

Why did the six eso children stay hypermetropic while the seven non-eso children with the same initial hypermetropia started to become emmetropic (Fig 2)? We know little about what factors are important for the so called emmetropisation process in a normal child. The concept of emmetropisation as a mechanism, regulating the refraction of the eye towards achieving the best possible acuity, has been discussed since the 1920s. Attention was then drawn to the fact that the number of emmetropes in the population was larger than could be expected from a normal distribution.[9 10] The concept of emmetropisation implies that refraction develops towards emmetropia from hypermetropia as well as from myopia and astigmatism. Evidence has accumulated during the last decades that refraction is controlled by visual input. Evans *et al*[11] recently reviewed animal experiment and human observations suggesting that defective emmetropisation is associated with deficient visual input or faulty neural transmission. Evans *et al*[11] have found that individuals with congenital achromatopsia have higher refractive errors than normal persons and also show a defective tendency to become emmetropic. They propose that retinal cones are involved in the feedback control of ocular refraction. Medina[7] suggests a mathematical model for a feedback loop which operates by detecting a refractive error and by correcting for it. This model implies that corrective lenses may have a negative effect on the emmetropisation process. He discusses the possibility that accommodation may be involved in the emmetropisation process as a feedback signal but offers no definite evidence for or against.

If accommodation is involved, it should be possible to influence it. Some reports for different species, including man, support the idea that conditions favouring near vision may induce myopia.[12–14] There have been several reports about the favourable effect of cycloplegics on stopping or at least delaying the progression of myopia,[15–17] and these results naturally focus attention on accommodation as a myopia enhancing factor. However, some recent observations challenge this theory. Pärssinen *et al*[18] have found a positive correlation between short reading distance and the development of myopia. But the progress of myopia could not be stopped by reducing accommodation. Dobson *et al*[19] have studied the effect of glasses on the development of hypermetropia in small children, and they suggest that wearing glasses decreases the normal reduction in hypermetropia. They argue that accommodation is involved as a factor promoting emmetropisation. McBrien and Barnes[20] have reviewed theories of refractive error development, and they discuss theories of the emmetropisation process and how to influence it through environmental factors. They emphasise the importance of research in this field, not least for practical reasons, in order the better to understand the development of refraction and to know whether, how, and when to interfere.

Is it possible in our study to implicate differences in accommodation as the reason for the differences in emmetropisation between the two hypermetropic groups, the eso and the non-eso groups? All children in the eso group got glasses but none before the age of 2. If we compare the two groups at the age of 2, the figures indicate that the emmetropisation process has started for the non-eso group by then (Fig 2, Table 1). Thus it seems that the glasses are not responsible for the failure to become emmetropic, at least not exclusively. Our results do not indicate what possible part accommodation may play in the development of refraction. Fabian[4] emphasises that the main changes towards emmetropia occur during the first two years of life. Our study confirms this. The process continues, however, in some individuals up to 4 years, and we do not yet know what happens after that age. We suggest that failure to become emmetropic is a significant factor to consider when determining the risks for strabismus, but we have no explanation to offer for this failure. Apart from the hypermetropia the eyes were completely normal, including the ocular fundi. All initially hypermetropic children whose emmetropia did not decrease started to squint. We certainly believe that the hypermetropia is essential for the strabismus. It could be that the failure to become emmetropic in itself has nothing to do with the strabismus. If the hypermetropia is large enough and, for instance, the fusional capacity is weak enough, the child may start to squint. But another explanation might be that some aberration in the refractive media is responsible for both the failure to become emmetropic and the development of strabismus. Sorsby *et al*[21 22] postulated a mechanism by which axial length, lens power, corneal power, and anterior chamber depth correlate with each other to produce emmetropia. Failure of this correlation process would produce moderate deviations from emmetropia, so called correlation ametropia. They found that in high hypermetropia and high myopia a single component, most frequently the axial length, was abnormal, and they used the expression 'component ametropia' for this group. Our results do not warrant a subdivision of the two different hypermetropic groups along these lines, since we do not have enough data about dimensions of the refractive media. Longitudinal studies from infancy to school age, including measurements of axial lengths and other refractive parameters, would be of great theoretical and practical importance. Better knowledge of how ocular refraction develops and what factors may interfere with this development is of great significance, not least for practical clinical work. We shall possibly have to change our practice in prescribing glasses and treating strabismus.

We have postulated that strabismus in the family indicates a substantial risk of strabismus in the child,[3] and this has been verified. Of the children in this group 17·6% developed a strabismus. We have found that those who start to squint are hypermetropic at the start of squint, have been equally hypermetropic since infancy, and will stay at the same level of hypermetropia at least until the age of 4. What practical conclusions may be drawn from these observations? We do not believe that refraction screenings of unselected groups of small children should be recommended. Screening involves many problems and great costs.[23 24] Our results show that there is a substantial group of children whose refractive errors at least during the first two years are very unstable, perhaps even longer. This means that it is hard to judge which children are at risk for developing strabismus and/or amblyopia on the basis of a single refraction.

We suggest that awareness of heredity and cooperation from parents should be considered when looking for strabismus and amblyopia. Parents could be questioned on some occasion during the programme for children's health care regarding strabismus in the family. Parents in squinting families could be encouraged to be observant and opportunities created to consult an ophthalmologist if problems arise and for a routine retinoscopy at about 2·5 years. At that age it should be possible to differentiate most of the children at risk from those in the normally emmetropising group judging from the height of the hypermetropia. We do not claim to be able to find all children at risk for amblyopia, but we believe that a substantial part might be discovered.

We should like to emphasise that the parents in our study made accurate and relevant observations after having been given some superficial instruction. Rosner and Rosner[26] have shown parents to be good detectors of strabismus. We suggest that they may be used actively in screening for strabismus.

This work was supported by research funds from the county council of Goteborgs and Bohus Province.

1 Kohler L, Stigmar G Vision screening in four-year-old children *Acta Paediatr Scand* 1973; **62**: 17–27.

2 Ingram RM Refraction as a basis for screening children for squint and amblyopia. *Br J Ophthalmol* 1977; **61**: 8–15

3 Ingram RM, Walker C, Wilson JM, Arnold PE, Dally S. Prediction of amblyopia and squint by means of refraction at age 1 year *Br J Ophthalmol* 1986; **70**: 12–5.

4 Fabian G. Ophthalmological serial examinations of 1200 children in their second year of life *Acta Ophthalmol (Kbh)* 1966; **49**: 473–9

5 Ingram RM, Barr A. Changes in refraction between the ages of 1 and 3 5 years. *Br J Ophthalmol* 1979; **63**: 339–42

6 Abrahamsson M, Fabian G, Sjostrand J Changes in astigmatism between the ages of 1 and 4 years· a longitudinal study. *Br J Ophthalmol* 1988, **72**: 145–9

7 Medina A. A model for emmetropization *Acta Ophthalmol (Kbh)* 1987; **65**: 565–71

8 Lennerstrand G. In Lennerstrand G, von Norden GK, Campos EC, eds. *Strabismus and amblyopia* Wenner-Gren International Symposium Series. London. Macmillan, 1987; **49**: 5–21

9 Wibaut F. Uber die emmetropisation und den Ursprung der spharischen Refraktionsanomalien *Graefes Arch Clin Exp Ophthalmol* 1925; **116**: 596–612.

10 Stromberg E Über Refraktion und Achsenlage des menschlischen Auges *Acta Ophthalmol (Kbh)* 1936; **14**: 281–91.

11 Evans NM, Fielder AR, Mayer DL. Ametropia in congenital cone deficiency-achromatopsia: a defect of emmetropisation? *Clin Vision Sci* 1989; **4**: 129–36

12 Rose L, Yinon U, Belkin M. Myopia induced in cats deprived of distance vision during development. *Vision Res* 1974; **14**: 1029–32

13 Young FA. The effect of restricted visual space on the primate eye *Am J Ophthalmol* 1961; **52**: 799–806

14 Young FA, Leary GA, Baldvin WR, *et al* The transmission of refractive errors within Eskimo families. *Am J Optom Physiol Opt* 1969; **46**: 676–85

15 Bedrossian RH The effect of atropine on myopia. *Ann Ophthalmol* 1971, **3**: 891–7.

16 Brenner RL Further observations on use of atropine in the treatment of myopia. *Ann Ophthalmol* 1985; **17**: 137–40.

17 Yen M-Y, Liu J-H, Kao S-C, Shiao C-H. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol* 1989; **21**: 180–7.

18 Parssinen O, Hemminki E, Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. *Br J Ophthalmol* 1989; **73**: 547–51

19 Dobson V, Sebris SL, Carlson MR. Do glasses prevent emmetropization in strabismic infants? *Invest Ophthalmol Vis Sci* 1986; **27** (ARVO suppl) 2

20 McBrien NA, Barnes DA A review and evaluation of theories of refractive error development. *Ophthalmic Physiol Opt* 1984; **4**: 201–13

21 Sorsby A, Benjamin B, Davey JB, Sheridan M, Tanner JM Emmetropia and its aberrations. *Med Res Council Sp Rep Ser* London: HMSO, 1957: no 23

22 Sorsby A The nature of spherical refractive errors. In: *Report of the workshop on refractive anomalies of the eye.* Washington, DC: US Department of Health, Education, and Welfare, 1967 NINDB.

23 Taylor D. Screening? *Trans Ophthalmol Soc UK* 1985; **104**: 637.

24 Ingram RM. Should pre-school children be screened for visual defects? *Trans Ophthalmol Soc UK* 1985; **104**: 646–7.

25 Rosner J, Rosner J. Parents as screeners for strabismus in their children. *J Visual Impairment Blindness* 1988, **83**: 193–4

Oertli/Rodenstock/Canon

Versatility/Innovation/Practicality

Oertli SonoCat & Vitro-Cat

The **Oertli** range of Swiss-made microsurgical systems is well represented by their SonoCat and Vitro-Cat instruments. The high quality precision of these systems is supplemented by innovative design such as the I/A cassette facility, and ease of sterilization. The computerised irrigation bottle hight control system is unique.

Scanning Laser Ophthalmoscope

Rodenstock's new revolutionary instrument allows real time imaging and recording of the fundus. Its innovative imaging technique enables the physician to evaluate retinal disease by visualising the retina in an unusually high contrast and with excellent resolution on a video monitor. The information may be stored on video for future reference and analysis.

Canon KU-1 Keratometer and A-Scan Ultrasound Biometer

A combined instrument for automatic Keratometry and Biometry from **Canon** complete with software and facility for determining IOL parameters. Easy to use, accurate and practical.

For a demonstration please phone our sales office.

Clement Clarke International Ltd
Airmed House, Edinburgh Way, Harlow, Essex CM20 2ED
Tel 0279 414969 Tlx 81338 Fax 0279 635232

PRESCRIBING INFORMATION

PRESENTATION

clear colourless solution in a plastic dropper bottle. lauline is available in two strengths containing 0.1% r 0.3% w/v metipranolol together with benzalkonium hloride 0.01% w/v as a preservative.

USES

lauline is a beta adrenoceptor blocking agent used in e topical treatment of chronic open-angle glaucoma nd other conditions in which intra-ocular pressure is levated above normal levels.

DOSAGE AND ADMINISTRATION

dults and the elderly: The recommended dosage is one rop instilled into the affected eye(s) twice daily.

hildren: Not Recomended.

ewly diagnosed patients with ocular hypertension or hronic open-angle glaucoma should be treated with lauline 0.1% [illegible] hanging to the higher strength if dequate contr[illegible]f intra-ocular pressure is not achieved r maintained. Patients on existing therapy, whether or ot this is to be continued, should receive Glauline 0.3%.

CONTRAINDICATIONS, WARNINGS, ETC

ontraindications: Bronchial asthma, history of ronchial asthma, chronic obstructive airways disease, inus bradycardia, second or third degree trio-ventricular block, cardiac failure, cardiogenic hock, hypersensitivity to any of the components of the reparation.

recautions and Warnings: As with other topically pplied beta-blockers, systemic absorption may occur iving adverse reactions similar to those of orally dministered beta-blockers. Cardiac and respiratory actions have been reported with topically applied eta-blockers including, rarely, death due to ronchospasm or cardiac failure. Congestive cardiac ilure should be adequately controlled before starting erapy with Glauline. If the patient has a history of rdiac disease, pulse rate should be monitored. iabetic control should be monitored during Glauline erapy in patients with labile diabetes. There have been ports of granulomatous anterior uveitis occuring in atients using Glauline. In any case, where a patient ows symptoms or signs suggestive of anterior uveitis, lauline should be withdrawn and an alternative ocular ypotensive agent substituted. Glauline contains nzalkonium chloride as a preservative and should erefore not be used in patients continuing to wear soft ydrophilic) c[illegible]tact lenses. Use in pregnancy: lthough ther[illegible]s no evidence to suggest that etipranolol has teratogenic properties, its use during regnancy should be avoided unless the potential enefits are considered to outweigh the possible hazards.

se in lactation: As beta-blockers can pass into breast ilk, consideration should be given to stopping reast-feeding if therapy with Glauline is considered ecessary.

ide-effects:

Ocular: Transient burning or stinging on instillation, lurred vision, superficial punctate keratitis, lepharoconjunctivitis and anterior uveitis have been ported.

Cardiovascular: Bradycardia and hypotension can ccasionally occur following the systemic absorption of pically applied beta-blockers.

Respiratory: Bronchospasm can occur, redominantly in patients with a history of reversible bstructive airways disease. Dyspnoea and respiratory ilure have also been reported with topically applied eta-blockers.

CNS: Headache, ataxia, weakness and lethargy can ccur.

Dermatological: Local manifestations of contact nsitivity reactions around the eyes can involve skin shes on the lower lids and cheeks, and peri-orbital edema.

rug interactions: Caution should be exercised if used conjunction with oral beta-blockers as additive effects systemic beta blockade may occur. Overdosage: verdosage is unlikely by the ocular route. If excess ug is accidentally administered to the eye, the affected e(s) should be immediately flushed with water or line. If accidental or deliberate systemic ingestion has ken place, bronchospasm, bradycardia, hypotension d cardiac failure may result, and treatment for verdosage of a beta-receptor blocking agent should be itiated.

PHARMACEUTICAL PRECAUTIONS

lauline should not be diluted or dispensed from any ntainer other than the original bottle. The unopened oduct has a shelf life of 3 years, but as with other eye ops the contents of each bottle should be discarded one onth after opening.

LEGAL CATEGORY POM

PACKAGE QUANTITIES

lauline is supplied as a sterile ophthalmic solution in a ml plastic dropper bottle.

FURTHER INFORMATION

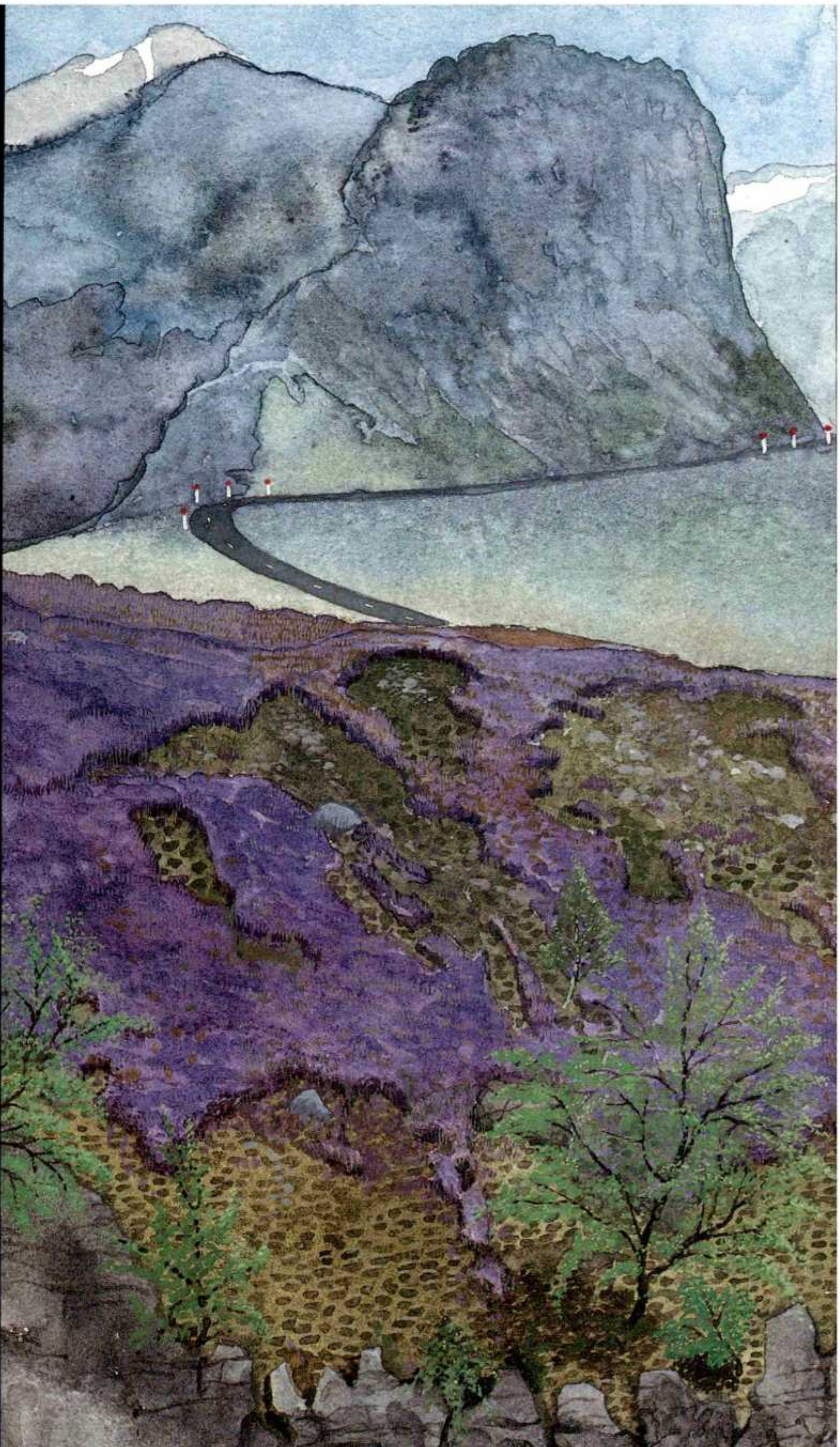
lauline reduces intra-ocular pressure with little or no fect on pupil size or accommodation. For newly agnosed glaucoma patients, clinical trial experience ggests that approximately 85% will achieve adequate ntrol of their intra-ocular pressure with Glauline 0.1%.

PRODUCT LICENCE NUMBERS

lauline 0.1% 0033/0104
lauline 0.3% 0033/0105

BASIC NHS PRICE

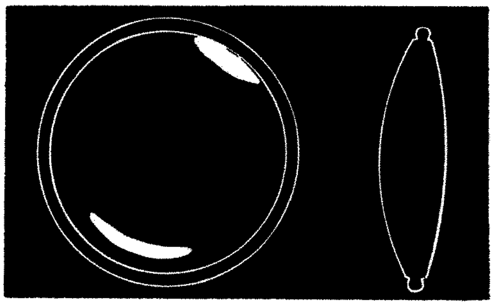
ml - 0.1% £4.03, 0.3% £4.67.



Glauline

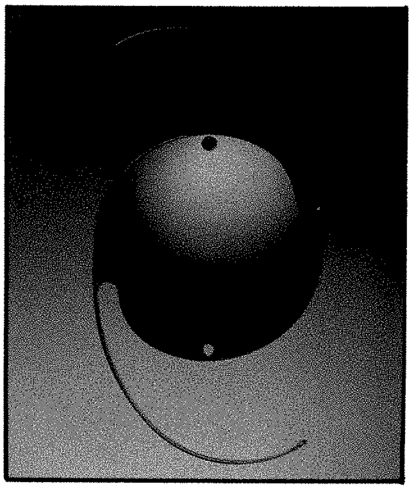
Smith & Nephew Pharmaceuticals Ltd

Bampton Road, Harold Hill,
Romford, Essex RM3 8SL, England
Telephone: Ingrebourne (04023) 4933
Telex: 898 058 SMINEPG
Fax: 04023 71316



In 1949 there was only one Intraocular lens manufacturer in the world ...

RAYNER



For many Ophthalmologists there still is.

For over 40 years Rayner have been manufacturing I.O.L's to meet the changing needs of the World's Ophthalmologists.

Rayner Intraocular Lenses Limited

1-2 Sackville Trading Estate, Sackville Road, Hove, East Sussex BN3 7AN ENGLAND
Telephone: (0273) 205401 (6 lines). Telex 877744 (RILSTE G). Fax: (0273) 24623

British Journal of Ophthalmology, 1990, 74, 595–600

Retinal arterial macroaneurysms: risk factors and natural history

Robert W Panton, Morton F Goldberg, Marilyn D Farber

Abstract

A case control study was conducted to identify the systemic and ocular risk factors for retinal arterial macroaneurysms. Forty-three patients with 52 photographically confirmed macroaneurysms were located. Forty-three age-matched, race-matched concurrent control patients were also identified. The patients with macroaneurysms had decreased visual acuity ($p<0.0001$) and a higher prevalence of hypertension ($p=0.037$), female sex ($p=0.099$), and retinal vein occlusions ($p=0.055$) than controls. In patients with both a macroaneurysm and venous occlusion there was a 12·0 times higher prevalence of macroaneurysms in the area of retina drained by the occluded vein ($p<0.05$). Common findings associated with macroaneurysms included retinal haemorrhage (81% of patients), retinal exudate (70%), vitreous haemorrhage (30%), macular involvement (30%), and distal arteriolar narrowing (26%). Arteriolar occlusion occurred spontaneously (8%) or after laser photocoagulation (16%).

Retinal arterial macroaneurysms are acquired dilatations of the retinal arterioles, usually occurring in the first three orders of the arteriolar tree.[1] Previous work has demonstrated a strong association between the development of macroaneurysms and several systemic factors. Most patients are over 60 years of age,[1 2] and 60–80% are women.[2-4] The large majority of patients have hypertension[3-5] and generalised atherosclerotic disease.[3 6] Other reported associations include hyperlipidaemia,[4 6] polycythaemia,[2] and cerebrovascular disease.[4 6 7]

No ocular risk factor for arterial macroaneurysms has been definitively confirmed. However, macroaneurysms have been reported in association with several diseases of the retinal vasculature, including retinal telangiectasia,[8] arterial emboli,[4 7] and retinal vein occlusion.[2 4 6 9]

Although many patients with macroaneurysms have been reported and several risk factors suggested, there has been no controlled study of risk factors. We therefore conducted a case control study to elucidate the ocular and systemic risk factors for the development of arterial macroaneurysms. We also investigated the natural history of macroaneurysms.

Department of Ophthalmology, University of Illinois at Chicago, USA
R W Panton
M F Goldberg
M D Farber

Correspondence to:
Robert W Panton, MD,
Department of
Ophthalmology, University
of Illinois at Chicago,
1855 W Taylor St, Chicago,
IL 60612, USA.

Accepted for publication
26 April 1990

Methods and materials

We reviewed the computerised diagnostic records from 1971 to 1988 of the Ophthalmic Photography Department of the University of Illinois at Chicago. A total of 43 patients with 52 arterial macroaneurysms were identified. The diagnosis was confirmed in every case with fundus photography demonstrating round, saccular, or fusiform dilatation of the retinal arterioles to greater than 100 µm. Intravenous fluorescein angiography was performed on 98% (42/43) of the patients.

Control patients were obtained for the study by review of random groups of 50 outpatient ophthalmic medical records to identify 43 control patients who were matched to the cases for the following variables: race, age within five years, and date of examination within three years. After control patients had been identified, the ipsilateral eye of cases and controls were matched.

A standardised history and physical examination form was used for new clinic patients, and data from cases and controls were obtained primarily from those forms. In patients with large vitreous haemorrhages, refraction and funduscopy were not performed at the initial examination but at subsequent examinations. Any case with missing data was included overall, but the case and corresponding control were excluded from analysis of the specific variable.

Hypertension was identified by prior diagnosis, by the use of systemic hypotensive medications, or by a blood pressure reading of over 140/90 mmHg at the time of examination.[10 11] Glaucoma was defined by history, by the use of ocular hypotensive drugs, or by the presence of raised intraocular pressure with characteristic optic nerve and visual field changes.[10] Other diseases, such as heart disease and diabetes, were identified by prior diagnosis or use of appropriate medications.

Statistical analysis was performed with the computerised statistical program True Epistat. Significance was tested with the χ^2 or Student's t test where appropriate. Two-tailed analyses were performed for all parameters except vision. All visual acuity data were converted to LogMAR scores[12] before a one-tailed Student's t test was performed. As a measure of the relative risk of getting a macroaneurysm with a potential risk factor present, odds ratios with Cornfield's 95% confidence limits were calculated.

Results

All cases were matched with controls for age, race, the eye (Table 1). The mean age was 69·7 years (range, 31–92 years) in the cases and 69·3 years in the controls. The racial distribution was the same in the cases and controls: 28 blacks, nine whites, and six Hispanics. The left eye was more commonly affected (63%), but the difference was not statistically significant ($p>0.05$).

A comparison of cases and controls by ocular and medical history is shown in Table 2. Hyper-

Table 1 Matched demographic variables in 43 case control pairs

Matched variable	*Cases*	*Controls*
Age (mean years)	69·7	69·3
Race: black	28	28
white	9	9
Hispanic	6	6
Eye: right	16	16
left	27	27

tension was present in 34 of 43 cases but in only 24 of 43 controls (p=0·037). The odds ratio (OR) for hypertension was 2·99, with 95% confidence limits of 1·1 and 8·7. Women were more prevalent in the cases than controls (OR=2·47) but with only marginal significance (p=0·099). Heart disease was also more common in the cases (OR=2·01), but the difference was not statistically significant (p=0·175). No association was found with the history of strabismus, glaucoma, arthritis, kidney disease, diabetic retinopathy, or diabetes. Analysis by stepwise logistic regression did not significantly affect the results.

The ipsilateral eye of cases and controls was matched for analysis of the ocular examination variables in Table 3. The mean best corrected visual acuity was 20/160 in the affected eye of the cases and 20/50 in the ipsilateral eye of the controls (p<0·0001). There were no significant differences between cases and controls for horizontal cup-to-disc ratio, intraocular pressure, or spherical equivalent.

Cases and controls had similar prevalences of strabismus, lens opacities, drusen, diabetic retinopathy, and corneal disease (Table 4). Retinal vein occlusion occurred in five of the cases but in none of the controls (p=0·055).

Table 2 Ocular and medical history of case control pairs

Historical variable	*Cases*	*Controls*	*p Value*	*Odds ratio*	*95% confidence interval*
Hypertension	34/43	24/43	0·037	2·99	(1·1–8·7)
Female sex	34/43	26/43	0·099	2·47	(0·86–7·2)
Heart disease	20/41	13/41	0·175	2·01	(0·76–5·4)
Strabismus	1/39	5/39	0·200	0·18	(0·02–1·7)
Glaucoma	2/40	5/40	0·432	0·37	(0·07–2·4)
Arthritis	20/38	21/38	1·000	0·90	(0·33–2·4)
Kidney disease	2/38	1/38	1·000	2·06	(0·18–23)
Diabetic retinopathy	4/43	3/43	1·000	1·37	(0·24–8·4)
Diabetes	7/41	7/41	1·000	1·00	NC*

*NC=not calculable.

Table 3 Mean values of ocular examination in case control pairs

Examination variable	*Number of pairs*	*Cases*	*Controls*	*p Value*
Visual acuity	43	20/160	20/50	<0·0001
Horizontal cup-to-disc ratio	39	0·38	0·34	0·19
Intraocular pressure (mmHg)	43	16	17	0·28
Spherical equivalent*	30	+0·86	+0·51	0·31

*Eleven aphakic and pseudophakic individuals were excluded from calculations of spherical equivalents.

Table 4 Prevalence of associated ocular disorders identified by examination of case control pairs

Historical variable	*Cases*	*Controls*	*p Value*	*Odds ratio*	*95% confidence interval*
Retinal vein occlusion	5/43	0/43	0·055	NC*	NC
Strabismus	3/43	5/43	0·356	0·57	(0·10–3·0)
Lens opacity	11/43	7/43	0·427	1·77	(0·55–5·8)
Drusen	6/43	4/43	0·738	1·58	(0·36–7·4)
Diabetic retinopathy	5/43	4/43	1·000	1·28	(0·27–6·3)
Corneal disease	2/43	1/43	1·000	2·05	(0·19–23)

*NC=not calculable.

Table 5 Clinical characteristics of 43 arterial macroaneurysms

Characteristic	*Number of patients*	*%*
Number of macroaneurysms:		
One	37	86
Two	5	12
Five	1	2
Location of macroaneurysms:		
Superotemporal	22	51
Inferotemporal	12	28
Superonasal	3	7
Inferonasal	0	0
Off optic nerve	6	14
Order of retinal artery:		
First	12	28
Second	22	51
Third	5	12
Fourth	3	7
Fifth	1	2

Detailed ophthalmoscopic examination was made of the five patients with both a macroaneurysm and venous occlusion. For example, in case 1 and in a non-detailed case the macroaneurysm followed the branch retinal vein occlusion in the same retinal quandrant three years and fourteen years later, respectively. In two other cases the macroaneurysm and retinal vein occlusion occurred in the same retinal quadrant, but the temporal relationship is unknown. The fifth patient had a hemiretinal vein occlusion and a macroaneurysm in different retinal areas. Overall the five patients with both a macroaneurysm and venous occlusion had a 12·0 times higher prevalence of macroaneurysms in the retinal area supplied by the occluded vein than in the remaining retinal area (p<0·05).

The characteristics of the macroaneurysms are shown in Table 5. A total of 86% of the patients presented with one macroaneurysm, 12% had two, and 2% had five. All 43 cases presented with unilateral macroaneurysms, but two patients had subsequent involvement of the other eye. Macroaneurysms usually presented superotemporally (51%) or inferotemporally (28%) and often occurred on the first three orders of the arteriolar tree. Most macroaneurysms were surrounded by retinal haemorrhage (81%) and exudate (70%). Macular exudate or haemorrhage (30%), vitreous haemorrhage (30%), distal arteriolar narrowing (26%), and arterial emboli (9%) were also observed.

Branch artery occlusion occurred spontaneously in two out of 24 individuals (8%) and after laser therapy in three out of 19 individuals (16%). Treatment of nine patients with argon laser photocoagulation directly to the macroaneurysm and surrounding retina resulted in two arteriolar occlusions. Direct aneurysmal treatment with dye yellow laser photocoagulation in five patients resulted in one arteriolar occlusion (case 1). No occlusions were seen in three patients treated with only perianeurysmal argon laser photocoagulation. None of the five branch artery occlusions had a major effect on visual acuity.

Case histories

CASE 1

A 63-year-old black female with a 15-year history of adult onset diabetes and systemic hyperten-

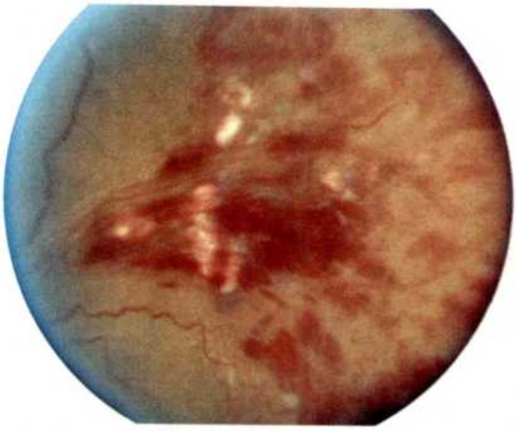


Figure 1A

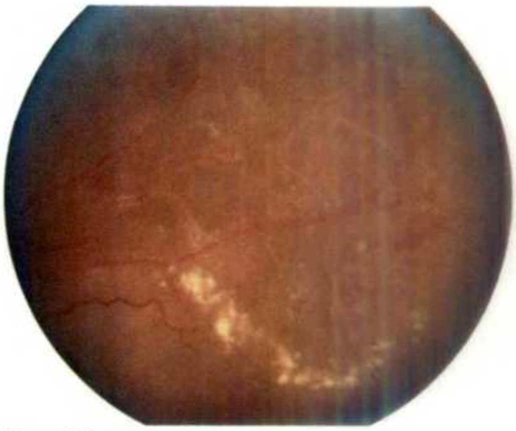


Figure 1C

sion complained of blurred vision in her left eye. Ocular examination demonstrated a best corrected visual acuity of 20/40 and a left superotemporal branch retinal vein occlusion (Fig 1A). Fluorescein angiography showed dilated retinal veins and large areas of hypofluorescence (Fig 1B). Two years later the haemorrhage cleared (Fig 1C), and the visual acuity returned to 20/20. The angiogram demonstrated capillary non-perfusion and remodelling (Fig 1D). Arteriolar irregularity was seen at the origin of dilated collateral vessels (arrow).

At the same location one year later there was a large arterial macroaneurysm with surrounding haemorrhage and exudate (Figs 1E, 1F). Because the exudate had encroached on the fovea and the visual acuity had dropped to 20/40, the patient received dye yellow laser photocoagulation (three applications, 577 nm wavelength, 600 μm spot size, 0·5 s duration, 170 mW intensity) directly to the macroaneurysm, sparing the feeding and draining segments of the arteriole.[13-15]

Two months after photocoagulation the foveal exudate increased, and the visual acuity dropped to 20/200. But six months later the haemorrhage and exudate resorbed, leaving a visual acuity of 20/25 (Fig 1G). The angiogram showed occlusion of the arteriole just proximal to the site of photocoagulation and retrograde filling of the distal arteriole through collateral vessels (Fig 1H).

CASE 2

A healthy 66-year-old white male presented with a best corrected visual acuity of 20/40 in the left eye, with two macroaneurysms of the superotemporal artery (Fig 2A). The second macroaneurysm was fibrotic and surrounded with haemorrhage and exudate. No laser photocoagulation was recommended. Two months later the proximal macroaneurysm obstructed, resulting in ischaemic swelling of the retina (Fig 2B) and a visual acuity of 20/60. Non-perfusion of the distal arteriolar segment was demonstrated with

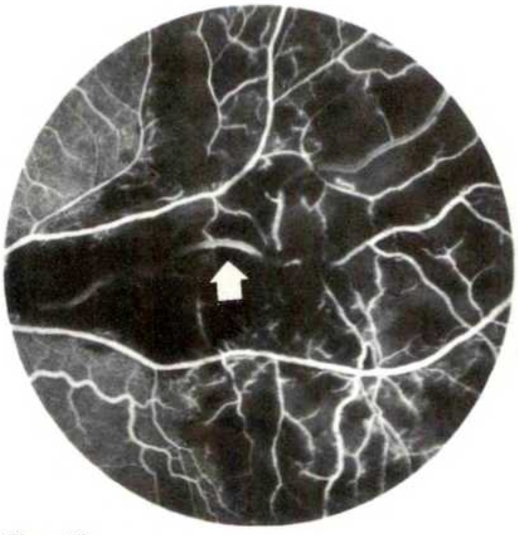


Figure 1B

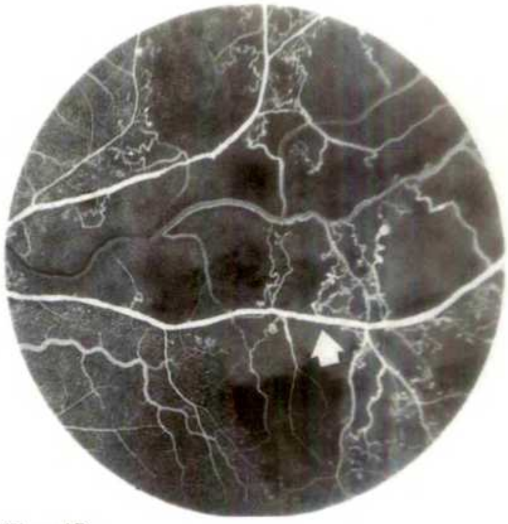


Figure 1D

Figure 1 A: Left superotemporal branch retinal vein occlusion. B: Corresponding fluorescein angiogram demonstrates a dilated retinal vein (arrow) and large areas of hypofluorescence. C: Two years later the haemorrhage has cleared, revealing lipid exudate, dilated capillaries, and sclerotic veins. D: Fluorescein angiography shows capillary non-perfusion and remodelling. Arteriolar irregularity is seen at the origin of dilated collateral vessels (arrow). E: One year later the same site has a large arterial macroaneurysm with surrounding haemorrhage and exudate. F: Angiography shows discrete filling of the macroaneurysm. G: Eight months after photocoagulation the haemorrhage resorbed, leaving foveal exudate. H: Fluorescein angiography demonstrates occlusion of the arteriole (arrow) just proximal to the site of photocoagulation. There is retrograde filling of the distal arteriole.

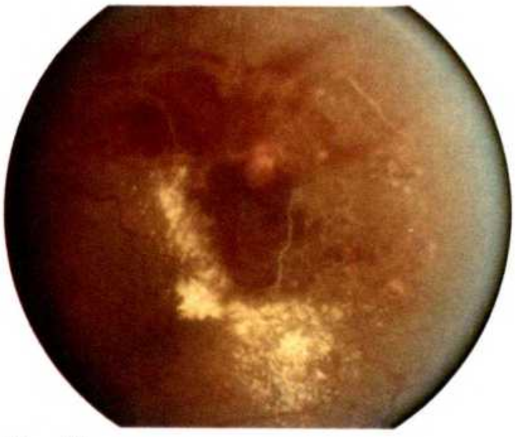


Figure 1E

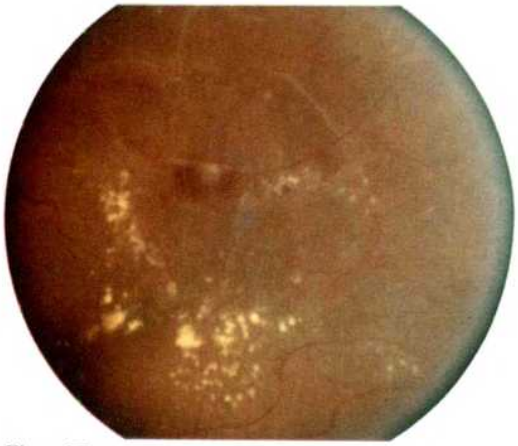


Figure 1G

fluorescein angiography (Fig 2C). Within six months both macroaneurysms had involuted, and the visual acuity returned to 20/40.

Discussion

Several studies have described the clinical characteristics of patients with macroaneurysms, but the patients were not compared with a control population.[3-8,15-18] We therefore undertook a case control study to identify the systemic and ocular risk factors for the development of macroaneurysms.

Arterial macroaneurysms are more common in elderly patients. The mean age of the cases in our study was 69·7 years. Histopathologically, aging of arterioles is characterised by an increase in intimal collagen and a replacement of medial muscle fibres with collagen.[2,19] The arterial wall becomes less elastic and more susceptible to dilatation from elevated hydrostatic pressure.[3]

Systemic hypertension and haemodynamic stress have been implicated in the pathogenesis of intracranial aneurysms.[20] Hypertension is also a significant risk factor for retinal arterial macroaneurysms, and 79% of our cases were hypertensive. Hypertension can lead to hyaline degeneration of vessel walls, loss of autoregulatory tone, and arterial dilatation.[21] Hypertensive patients also have raised hydrostatic pressures. According to the Laplace equation, a raised transmural pressure is directly proportional to a raised wall tension, which might predispose to macroaneurysm formation.[20]

Venous occlusion was more common in the patients with macroaneurysms. A statistical association between the two diseases may be explained by several possibilities: (*a*) Both diseases may have similar risk factors, such as age and hypertension.[10,11] (*b*) Venous occlusion may be caused by an adjacent macroaneurysm.[2] Or (*c*) a macroaneurysm may result from venous occlusion. The last possibility could occur when chronic venous stasis leads to local arterial thrombosis, endothelial damage, and aneurysm formation.[7] Alternatively, a macroaneurysm following venous occlusion could form at the origin of a dilated collateral vessel, as occurred in case 1. A macroaneurysm might arise at such a location because of arterial wall weakness or local turbulent flow.[2,7,18] Although the present study does not distinguish among these possibilities, the apparently common occurrence of macroaneurysms and venous occlusions in the same retinal area suggests the influence of local factors.

Females were more prevalent among cases (79%) than controls (60%), but the relatively small sample size was insufficient to document statistical significance. Several series have previously reported that women represent the large majority of patients with macroaneurysms;

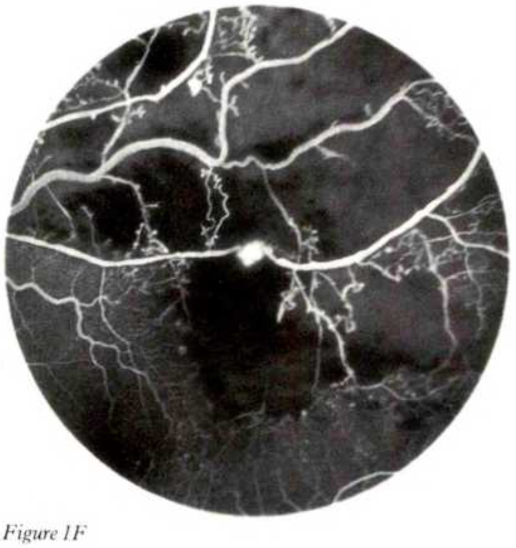


Figure 1F

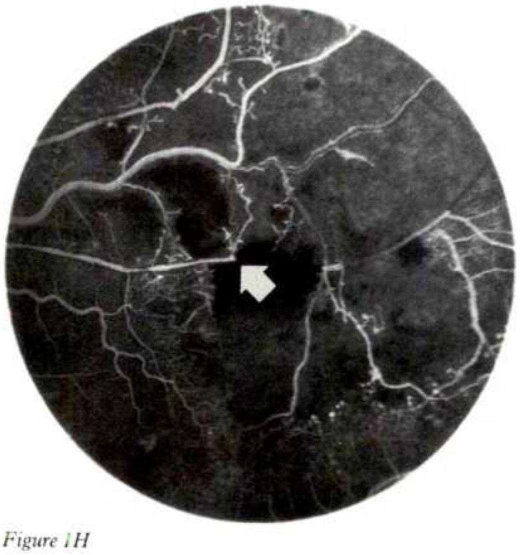


Figure 1H

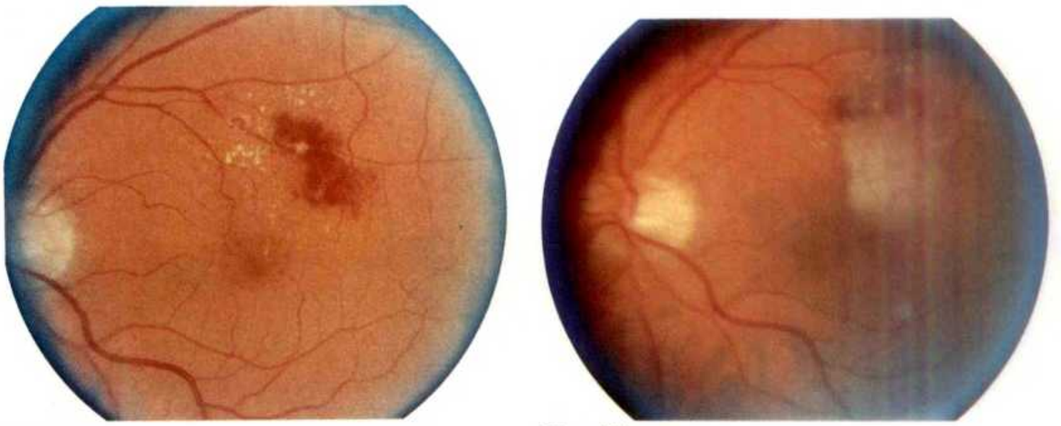


Figure 2A

Figure 2B

Figure 2 A: Left eye, two superotemporal arterial macroaneurysms. The distal macroaneurysm is fibrotic and surrounded with haemorrhage and exudate. B: Two months later obstruction of the proximal macroaneurysm leads to ischaemic swelling of the retina. C: Angiography demonstrates distal arteriolar non-perfusion.

however, the significance of the observation is uncertain because no control groups were provided.[2-8,15,16,19] Intracranial saccular aneurysms, particularly those on the internal carotid artery, are also more common among women.[20] This female preponderance has been attributed to both heritable and hormonal causes.[20]

Our retrospective analysis was limited to a standardised history and physical examination form, and we were unable to analyse potential risk factors such as cerebrovascular disease, atherosclerosis, polycythaemia, and hyperlipidaemia. Our study was also unable to evaluate microvascular risk factors such as arterial emboli and plaques in a controlled fashion, because only the cases underwent fluorescein angiography. Despite these inherent limitations, our study showed that patients with arterial macroaneurysms also have an increased prevalence of other vascular changes, both systemically (for example, hypertension and aging) and locally (for example, retinal vein occlusions).

In addition to examining risk factors we began a preliminary study of the natural history and therapy of macroaneurysms. Arteriolar occlusion was seen spontaneously in 8% of patients and after laser photocoagulation in 16% of patients. No occlusions were seen after exclusively perianeurysmal laser treatment. Several authors have suggested that arteriolar obstruction may be more common after direct aneurysmal rather than perianeurysmal photocoagulation.[16,17,22]

In the largest series of patients to receive dye yellow laser photocoagulation for macroaneurysms Joondeph and colleagues reported that no arterial occlusions occurred after treatment of 12 patients.[15] However, our case 1 had an arterial occlusion after dye yellow photocoagulation with an identical treatment protocol. Arterial occlusions may not be readily apparent by ophthalmoscopy, possibly because of distal collateral flow. Fluorescein angiography after laser treatment of macroaneurysms might reveal a higher incidence of branch artery occlusions than previously believed.

To follow up our retrospective analysis of macroaneurysm risk factors we are now prospectively observing our patients with photography and angiography to determine the rates of involution of macroaneurysms, resorption of haemorrhage and exudate, and occlusion of arterioles.

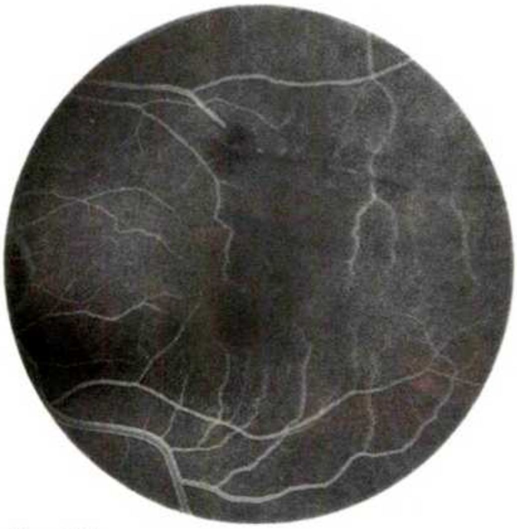


Figure 2C

The authors thank Mr Norbert Jednock and the Ophthalmic Photography Department for their assistance. This work was supported in part by training grant 7038 and core grant 1792 from the National Eye Institute, Bethesda, Maryland, and by unrestricted grants from the Alcon Research Institute, Fort Worth, Texas, and Research to Prevent Blindness, Inc, New York, New York.

1 Robertson DM. Macroaneurysm of the retinal arteries. *Ophthalmology* 1973; **77:** 55–67.
2 Lavin MJ, Marsh RJ, Peart S, Rehman A. Retinal arterial macroaneurysms: a retrospective study of 40 patients. *Br J Ophthalmol* 1987; **71:** 817–25.
3 Rabb MF, Gagliano DA, Teske MP. Retinal arterial macroaneurysms. *Surv Ophthalmol* 1988; **33:** 73–96.
4 Palestine AG, Robertson DM, Goldstein BG. Macroaneurysms of the retinal arteries. *Am J Ophthalmol* 1982; **93:** 164–71.
5 Abdel-Khalek MN, Richardson J. Retinal macroaneurysm: natural history and guidelines for treatment. *Br J Ophthalmol* 1986; **70:** 2–11.
6 Cleary PE, Kohner EM, Hamilton AM, Bird AC. Retinal macroaneurysms. *Br J Ophthalmol* 1975; **59:** 355–61.
7 Lewis RA, Norton EWD, Gass JDM. Acquired arterial macroaneurysms of the retina. *Br J Ophthalmol* 1976; **60:** 21–30.
8 Asdourian GK, Goldberg MF, Jampol L, Rabb MF. Retinal macroaneurysms of the retina. *Br J Ophthalmol* 1976; **60:** 21–30.
9 Panton RW, Goldberg MF. Risk factors of retinal arterial macroaneurysm. *Invest Ophthalmol Vis Sci* (ARVO abstracts) 1989; **30** (suppl): 476.

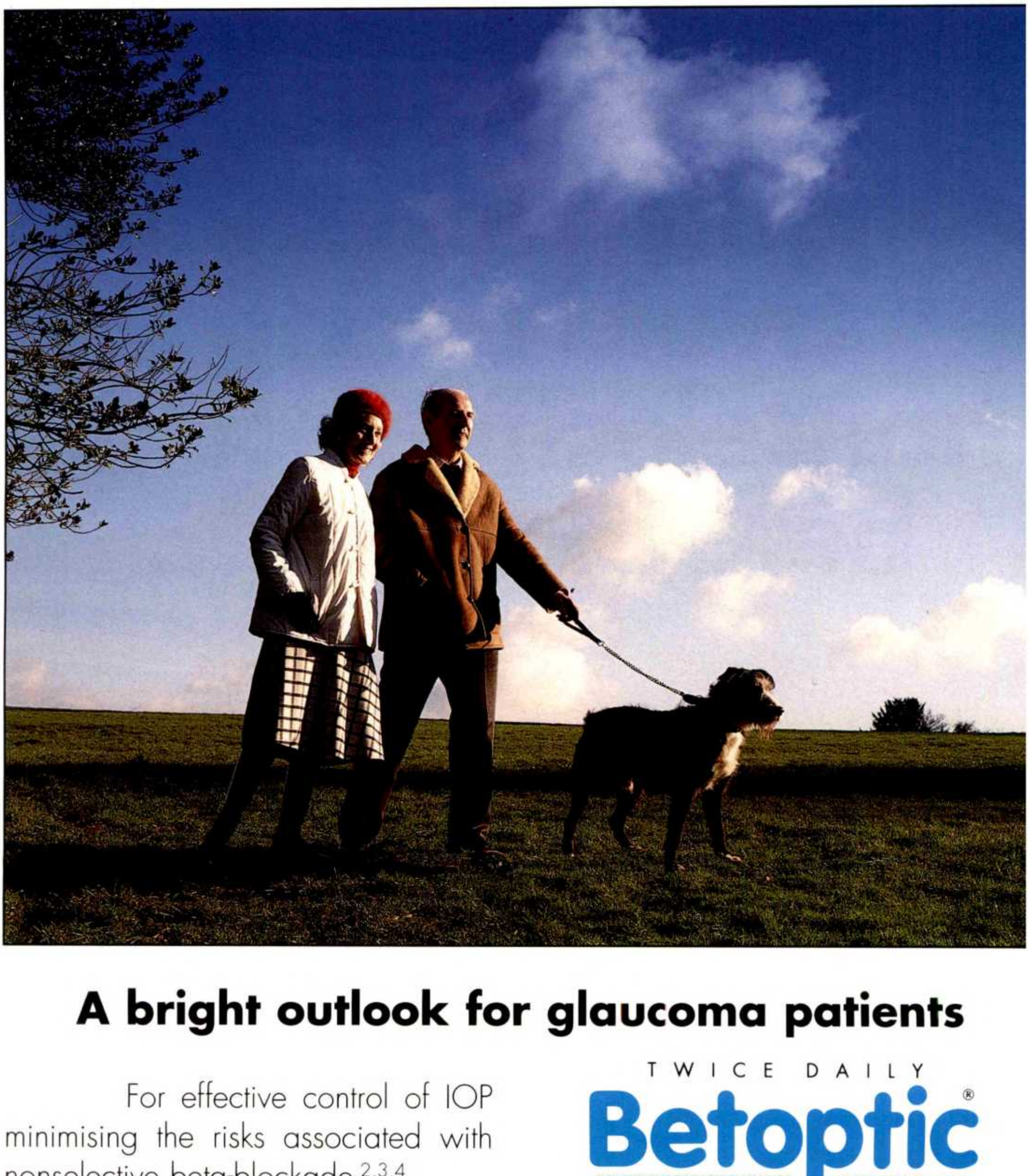
10 Johnston RL, Brucker AJ, Steinmann W, Hoffman ME, Holmes JH. Risk factors of branch retinal vein occlusion. *Arch Ophthalmol* 1985; **103**: 1831–2.
11 Apiah AP, Trempe CL Risk factors associated with branch vs. central retinal vein occlusion. *Ann Ophthalmol* 1989; **21**: 153–7
12 Ferris FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research *Am J Ophthalmol* 1982; **94**: 91–6.
13 Russell SR, Folk JC. Branch retinal artery occlusion after dye yellow photocoagulation of an arterial macroaneurysm. *Am J Ophthalmol* 1987; **104**: 186–7
14 Mainster MA, Whitacre MM. Dye yellow photocoagulation of retinal arterial macroaneurysms. *Am J Ophthalmol* 1988; **105**: 97–8.
15 Joondeph BC, Joondeph HC, Blair NP. Retinal macroaneurysms treated with the yellow dye laser. *Retina* 1989; **9**: 187–92.
16 Nadel AJ, Gupta KK. Macroaneurysm of the retinal arteries. *Arch Ophthalmol* 1976; **94**: 1092–6.
17 François J. Acquired macroaneurysm of the retinal arteries. *Int Ophthalmol* 1979; **1**: 153–61.
18 Khalil M, Lorenzetti DWC. Acquired retinal macroaneurysms. *Can J Ophthalmol* 1979; **14**: 163–9.
19 Garner A, Klintworth G *Pathobiology of ocular disease* New York: Dekker, 1982: 1480–525
20 Sekhar LN, Heros RC Origin, growth, and rupture of saccular aneurysms: a review *Neurosurgery* 1981; **8**: 248–60.
21 Tso MOM, Jampol LM. Pathophysiology of hypertensive retinopathy *Ophthalmology* 1982; **89**: 1132–45
22 Van Nouhuys E, Deutman AF Argon laser treatment of retinal macroaneurysms. *Int Ophthalmol* 1980; **2**: 45–53

For those patients who should avoid taking nonselective ocular beta blockers...

> “Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”[1]

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective



A bright outlook for glaucoma patients

For effective control of IOP minimising the risks associated with nonselective beta-blockade [2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only β_1 selective ocular beta blocker

SELECTIVE β_1 BETA-BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased co sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depre neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies not demonstrated any specific hazard there are no adequate and well-controlled studies in preg women. Because animal studies are not always predictive of human response this drug should be during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known wh Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is adminis to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml droptainer **PRODUCT LICE HOLDER AND NUMBER:** Alcon Laboratories U.K 0649/0097. DATE OF PREPARATION: JANUARY

Further information is available on request

Alcon

SPECIALISTS IN EYE CARE

Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

REFERENCES: 1. Jones FL, Ekberg NL. Letter N Eng J Med 1979; **301**: 270.

3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92

British Journal of Ophthalmology, 1990, 74, 601–604

The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma

John F Pitts, Jeffrey L Jay

Tennent Institute of Ophthalmology, University of Glasgow, Western Infirmary, 38 Church Street, Glasgow G11 6NT
J F Pitts
J L Jay

Correspondence to Dr J L Jay

Accepted for publication 3 May 1990

Abstract

A series of 24 patients with Fuchs's dystrophy are presented in whom detailed clinical measurement showed an association with axial hypermetropia and shallow anterior chamber. In 14 of these patients one cornea had developed oedema, of which 11 had required penetrating keratoplasty. Comparison of these eyes with the fellow eyes without corneal oedema revealed that the anomalies in measurement were not due to the process of decompensation. These 14 patients were then compared with the remaining 10 patients without corneal oedema in either eye, and a similar profile of anomalous measurements was observed. The whole group of 24 patients were then compared with three separate control groups, and in each case a significant trend towards hypermetropia, short axial length, and shallow anterior chamber was noted. The mean spherical equivalent refractive error in the patients with Fuchs's dystrophy was +2·48 D compared with −0·31 D for controls; corresponding means for axial length were 22·1 mm compared with 23·4 mm; and for anterior chamber depth were 2·2 mm compared with 2·7 mm. Each of these differences was statistically significant, but there was no significant difference for the keratometry measurements between patients and controls. Five of 24 (21%) of the patients had problems related to shallow anterior chambers of whom 3 (12%) had manifest angle closure glaucoma requiring surgical peripheral iridectomy. The aetiology of Fuchs's dystrophy and of ametropia is discussed and possible modes of association outlined. This previously unrecognised association gives a rational basis for the widely accepted practice of combining penetrating keratoplasty with lens extraction and has several other practical implications which are important in the differential diagnosis and treatment of Fuchs's dystrophy and angle closure glaucoma.

Fuchs's endothelial dystrophy accounts for about 10% of penetrating keratoplasties in series conducted in Europe and the USA.[1,2] Most authors advocate combined keratoplasty and lens extraction in this condition.[3-7] A few offer as an explanation an increased risk of angle closure glaucoma,[2,5,8] and one goes as far as to state that the Fuchs's dystrophy patients tend to have shallow anterior chambers.[9]

It had been noted that most of the patients attending the external eye diseases clinic of the Tennent Institute of Ophthalmology with Fuchs's endothelial dystrophy were hypermetropic and several had had associated complications such as acute angle closure glaucoma. We could find no published analysis of this possible association, though Bigar and Witmer[10] reported an unusually high incidence of bilateral endothelial dystrophy in a series of patients who had sustained a unilateral attack of angle closure glaucoma. Fuchs himself[11] did not comment on such an association, but he gives details of refraction on five of his 13 cases, and we have calculated a mean spherical equivalent of +2·45 D in these. We therefore carried out a retrospective study to determine if there was a significant association.

Materials and methods

All patients with Fuchs's dystrophy attending the External Eye Clinic were re-examined and the diagnosis confirmed in each case. Two categories of patient were identified:

(*a*) Patients with bullous keratopathy; most of these had required penetrating keratoplasty and the diagnosis had been confirmed histologically, but a few were still being managed conservatively.

(*b*) Patients without bullous keratopathy but with the diagnostic endothelial changes of Fuchs's dystrophy. Because of the controversy in classification of Fuchs's dystrophy as a distinct disease versus an extreme in a spectrum of age related change[12,13] our study required slit-lamp identification of confluent central cornea guttata both on retroillumination and specular reflection.

The following details were recorded for each patient: age; sex; spectacle refraction (past and present); age at first reading correction; history of amblyopia or childhood squint; history of angle closure glaucoma or peripheral iridectomy; keratometry; ultrasonic A-scan biometry of anterior chamber depth and axial length.

Spectacle Refraction. The current refraction was recorded and compared with the past prescriptions obtained from opticians' records or focimeter readings of the patients' oldest distance spectacles. This was done to identify cases of progressive refractive error caused by changes in the crystalline lens with age.

Amblyopia, squint, angle closure glaucoma, peripheral iridectomy. Information was obtained from the case records and confirmed at the time of re-examination.

Keratometry. Corneal radius was measured with the Javal-Schiøtz keratometer and the mean value was used for analysis. Readings obtained after keratoplasty or cataract surgery and in eyes with corneal oedema were not used.

Ultrasound biometry. Anterior chamber depth measurements were made with the Radionics Model 3000 Echo-Oculometer. Values following keratoplasty or cataract surgery and in eyes with corneal oedema were excluded. Axial length measurements were obtained with the same instrument. A mean of three readings was used providing the discrepancy between each reading did not exceed 0·1 mm. Where the eye was aphakic or pseudophakic, the appropriate correction factor was applied.

Results for the study patients were compared with those for age and sex matched controls attending with other diagnoses. Controls were separately analysed in groups according to source, namely: (i) patients admitted for cataract surgery; (ii) a mixture of general ophthalmology clinic patients; (iii) patients with primary open angle glaucoma attending the glaucoma clinic. Patients with either Fuchs's dystrophy or angle closure glaucoma were excluded from each control group, as were those whose sole reason for attendance was refractive error. A total of 72 controls (24 in each group) was studied.

Eyes with corneal oedema or previous cataract extraction or keratoplasty were compared with their fellow eyes (paired *t* test) to ensure that the process of corneal decompensation or surgery had not contributed to the development of hypermetropia and other features. The group of patients with corneal oedema or previous surgery was then compared with those without oedema in either cornea (unpaired *t* test) to ensure that patients with and without corneal oedema were part of a uniform population which might then be treated as a single group for analysis. For this comparison the mean value for the two eyes of each patient was used unless only one result existed for a pair of eyes. This method of comparison is acknowledged to give the lowest frequency of false positive associations and to have greater statistical precision than single eye comparisons or use of data from both eyes to double the sample size.[14] A similar method was used in comparing Fuchs's dystrophy patients with controls. The whole group of 24 patients with Fuchs's dystrophy was then compared with each of the three control groups (*t* test) and with the combined control population by analysis of variance.

Results

There were 24 patients who fulfilled the criteria for diagnosis of Fuchs's dystrophy and who were available for re-examination. Fourteen had developed bullous keratopathy in one eye, and, of these, 11 had required a penetrating keratoplasty and three were being managed conservatively. The other 10 patients, although showing the diagnostic endothelial changes, had no corneal oedema in either eye. Both eyes of each patient fulfilled the diagnostic criteria, but not all measurements were available for all eyes, because keratoplasty, cataract extraction, or bullous keratopathy prevented readings valid for the intrinsic state of the eye. Therefore values for refraction (2 eyes), axial length (5 eyes), keratometry (15 eyes), and anterior chamber depth (20 eyes) remained undetermined.

Eyes with corneal oedema closely matched the fellow eyes of the same patients for refraction and axial length (paired *t* test, $p>0{\cdot}5$, $n=14$ for refraction and 11 for axial length). In addition the 14 patients with corneal oedema were compared with the 10 patients without corneal oedema (*t* test) with no significant difference for age ($0{\cdot}2<p<0{\cdot}5$), refraction ($0{\cdot}2<p<0{\cdot}5$), axial length ($p>0{\cdot}5$), and anterior chamber depth ($0{\cdot}05<p<0{\cdot}1$). It seemed appropriate, there-

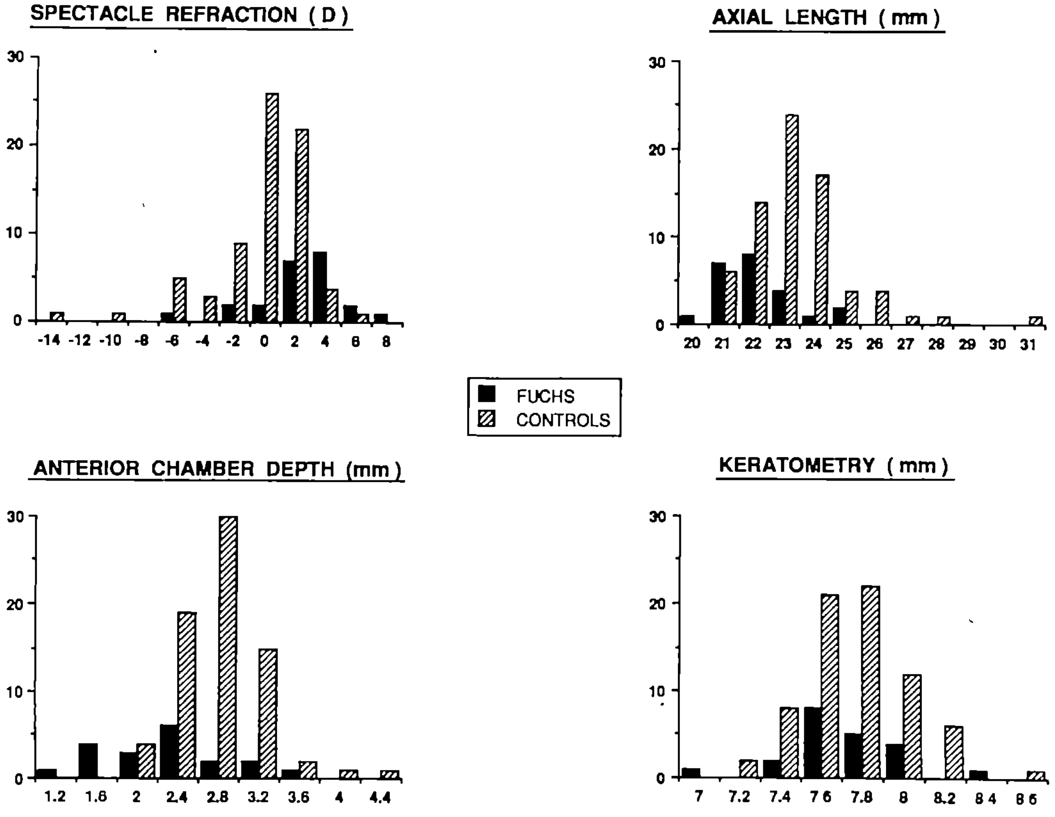


Figure 1 Histograms showing the refractive error, axial length, anterior chamber depth, and keratometry readings of 24 patients with Fuchs's dystrophy plotted alongside 72 control patients.

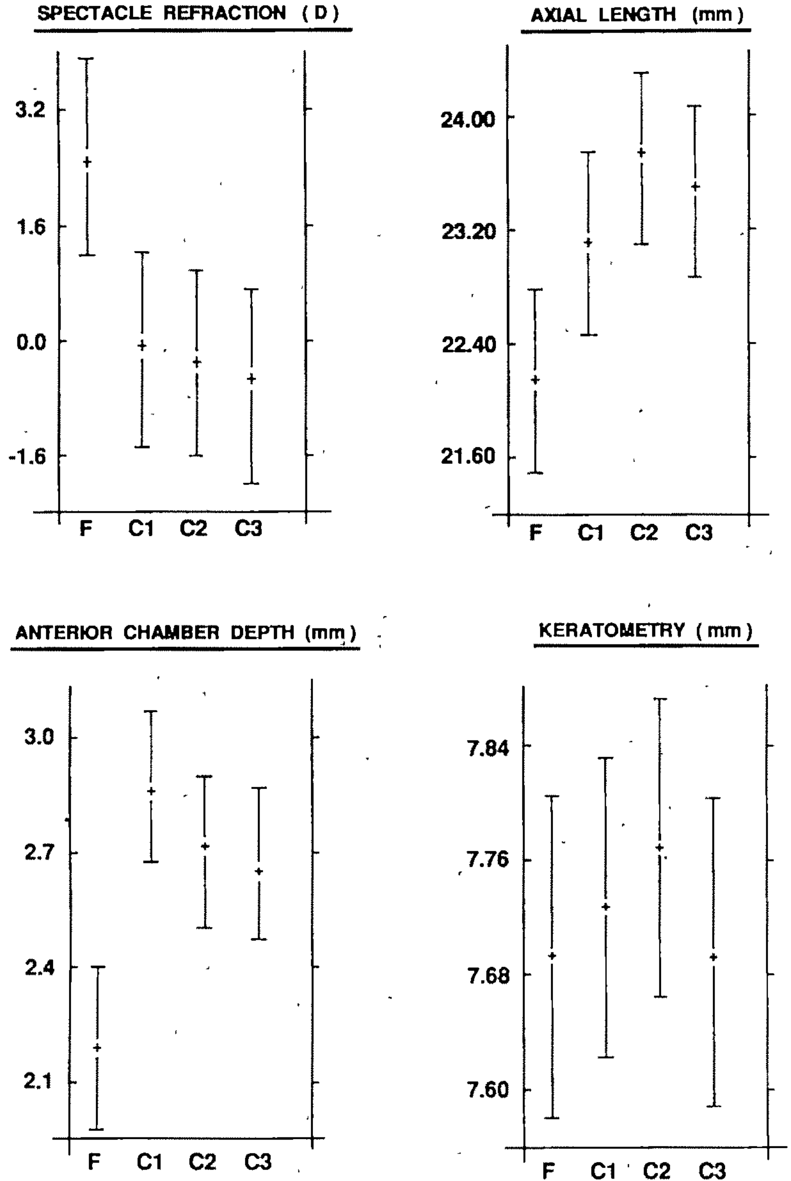


Figure 2 95% Confidence intervals (mean±2 SEM) for the refractive error, axial length, anterior chamber depth, and keratometry readings of 24 patients with Fuchs's dystrophy and 24 patients in each of 3 separate control groups. F=Fuchs's dystrophy; C1=patients admitted for cataract surgery; C2=a mixture of general ophthalmology clinic patients; C3=patients with primary open angle glaucoma attending the glaucoma clinic.

fore, to conclude that all 24 patients could be treated as a single group for analysis.

Figure 1 is a histogram showing the Fuchs's dystrophy patients plotted alongside the combined control population. They appear more hypermetropic with shorter axial length and shallower anterior chambers, but similar keratometry values, compared with the controls. The 24 patients with Fuchs's dystrophy were then compared statistically with each of the three control groups and there was a significant difference in all measurements (unpaired *t* test, $p<0{\cdot}001$ or $0{\cdot}001<p<0{\cdot}01$) except keratometry ($p>0{\cdot}5$). These comparisons are shown in Figure 2 with 95% confidence intervals (mean±2 SEM).

In addition to the statistical evidence for an association a high prevalence of the three main complications of hypermetropia was detected in the Fuchs's dystrophy patients.

(i) *Angle closure glaucoma.* Five of 24 (21%) had clinical problems related to shallow anterior chamber. Three of these (12% of total) had spontaneous attacks of angle closure glaucoma requiring surgical iridectomy. While this cannot be compared with the control group (as angle closure glaucoma was excluded), it is well in excess of the quoted incidence of 0·5%.[15 16] The remaining two were noted to have a shallow anterior chamber following keratoplasty.

(ii) *Amblyopia.* Four of our 24 patients (17%) had an amblyopic eye compared with two of the 72 controls (3%).

(iii) *Early presbyopia.* Nine of 24 (38%) of our patients with Fuchs's dystrophy required reading correction under the age of 30 years compared with nine of 72 (12%) of the controls.

Discussion

The association of hypermetropia with shallow anterior chamber and angle closure glaucoma seems agreed. Tomlinson and Leighton[17] found a mean anterior chamber depth of 2·31 mm in patients with primary angle closure glaucoma compared with 3·08 mm for controls; the corresponding mean axial lengths were 22·06 versus 22·58 mm. Our results show that Fuchs's dystrophy is associated with axial hypermetropia and shallow anterior chamber, which provides a link with the increased risk of angle closure glaucoma.

It is interesting to speculate on the nature of the relationship between Fuchs's dystrophy and axial hypermetropia. It is unlikely that the endothelial dystrophy leads to axial hypermetropia, as hypermetropia is known to develop in early life while Fuchs's dystrophy tends to become manifest over the age of 50. Nevertheless Lorenzetti *et al*[13] have demonstrated a surprisingly high incidence of cornea guttata in early life, and Rodrigues and others[18] have shown by electron microscopy that the changes in the posterior collagenous layer of Descemet's membrane can be detected as early as the first two decades. Therefore this possibility cannot be excluded entirely. It is difficult to conceive a mechanism whereby axial hypermetropia might cause endothelial dystrophy, and indeed not all cases of Fuchs's dystrophy have this refractive error. Complications such as manifest or subclinical episodes of angle closure and effects of contact lens wear may aggravate the endothelial abnormality but are unlikely to be its cause. We believe that a causal relationship (in either direction) is improbable and that the association arises from a common factor giving rise to both conditions by genetic linkage.

The inheritance of Fuchs's dystrophy is not resolved, but the weight of evidence favours autosomal dominance with variable penetrance.[7 19] The inheritance of refractive errors is equally controversial, with the most illuminating work on the subject being that of Sorsby,[20] who considered emmetropia to be the result of co-ordinated regulation of the individual components of refraction. For example, in 107 emmetropic eyes (0 to +0·50 D) he found an axial length of 22·3 to 26·0 mm, the eyes being emmetropic because of automatic adjustment of other components of refraction, mainly the corneal curvature. In 255 eyes with ametropia within the range +6 to −4 D, he found that 235 had axial length values within the range of the emmetropic group (22·3 to 26·0 mm) and that these were ametropic because of failed adjustment, mainly in terms of corneal curvature; he calls this group the correlation ametropias. Another 46 ametropic eyes, with more than +6 or −4 D, almost all had an axial length outside the range of 22·3 to 26·0 mm; these are ametropic due to a single abnormal value, commonly the axial length; this group he terms the component ametropias. From twin and family studies he concludes that emmetropia and correlation ametropia are inherited in a polygenic manner, while component ametropia is most likely to be monofactorial.

If we assume that our patients were correlation ametropes, then it seems that the mechanism for regulating corneal curvature has failed. This might indicate either genetic linkage between the polygene system for corneal curvature and Fuchs's dystrophy or that the endothelium is somehow involved in regulating corneal curvature and that an inherited endothelial abnormality prevents this from occurring, the same inherited anomaly later becoming manifest as Fuchs's dystrophy. If on the other hand our patients are component ametropes, there may be genetic linkage between the (monofactorial) inheritance of an abnormal axial length and the (monofactorial) inheritance of Fuchs's dystrophy.

In fact of the 33 hypermetropic eyes in our patients 25 (76%) have an axial length below 22·3 mm compared with only 29% in hypermetropic control eyes. While we accept that our axial length measurements cannot be directly statistically compared with Sorsby's, these findings are nevertheless strongly suggestive that a high proportion of our patients are what Sorsby terms component ametropes and that the second hypothesis of genetic linkage between two dominant genes is more likely.

While we have shown that Fuchs's dystrophy is frequently associated with hypermetropia and its risks, we cannot estimate from our data the frequency of Fuchs's dystrophy in hypermetropia. Bigar and Witmer[10] noted that 35% of patients with angle closure glaucoma had bilateral endothelial dystrophy. If this is so, it is highly significant, as it means that the patients who are subject to angle closure glaucoma tend to have an endothelium which is vulnerable to damage from the attack.

The association of Fuchs's dystrophy with axial hypermetropia has practical implications. Acute angle closure glaucoma and Fuchs's dystrophy may be confused as pain, glare, haloes, blurring of vision, and a shallow anterior chamber may be present in both conditions. Indeed mydriasis for examination or treatment of patients with Fuchs's dystrophy may precipitate angle closure in eyes with the shallowest anterior chambers.

The increased risk of shallow anterior chamber following penetrating keratoplasty for Fuchs's dystrophy justifies the practice of removing the crystalline lens during the operation. Waring *et al*[9] have stated that these patients benefit from a posterior chamber intraocular lens, and we prefer the Pearce tripod lens, a rigid design which prevents the anterior chamber from becoming shallow postoperatively.[21] With the increased frequency of hypermetropia, biometry to calculate the required power of intraocular lens is important, but keratometry may be impossible once bullous keratopathy has developed. Biometry should therefore be performed early in the course of the disease.

We thank Dr Donald Allan and Dr Gordon Murray for statistical advice and Susan Laing for preparing the illustrations

1 Lang GK, Naumann GO The frequency of corneal dystrophies requiring keratoplasty in Europe and the USA *Cornea* 1987, 6: 209–11

2 Waring GO III, Rodrigues MM, Laibson PR. Corneal dystrophies II. Endothelial dystrophies. *Surv Ophthalmol* 1978, 23: 147–68.

3 Dohlman CH, Hyndiuk RA Subclinical and manifest corneal oedema after cataract extraction In: Castroviejo, *et al*, eds. *Symposium on the cornea Trans New Orleans Acad Ophthalmol.* St Louis: Mosby, 1972; chapter 17 214–35

4 Arentsen JJ, Laibson PR Penetrating keratoplasty and cataract extraction combined vs nonsimultaneous surgery *Arch Ophthalmol* 1978; 96: 75–6

5 Waring GO III, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function *Ophthalmology* 1982, 89: 531–90

6 Polack FM. Glaucoma in keratoplasty. *Cornea* 1988; 7: 67–9.

7 Wilson SE, Bourne WM. Fuchs' dystrophy *Cornea* 1988; 7: 2–18.

8 Fine M Round table discussions. In: Castroviejo R, *et al*, eds *Symposium on the cornea Trans New Orleans Acad Ophthalmol.* St Louis: Mosby, 1972: 253–93

9 Rice NS Keratoplasty in bullous keratopathy In Casey TA, ed. *Corneal grafting*. London: Butterworths, 1972. chapter 10

10 Bigar F, Witmer R Corneal endothelial changes in primary acute angle closure glaucoma *Ophthalmology* 1982; 89: 596–9.

11 Fuchs E. Dystrophia epithelialis corneae *Graefes Arch Clin Exp Ophthalmol* 1910, 76: 478–508

12 Goar EL Dystrophy of the corneal endothelium (cornea guttata) with a report of a histological examination *Am J Ophthalmol* 1934; 17: 215–21.

13 Lorenzetti DN, Uotila MH, Parikh N, Kaufman HE. Central cornea guttata, incidence in the general population. *Am J Ophthalmol* 1967; 64: 1155–8

14 Newcombe RG, Duff GR Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies. *Br J Ophthalmol* 1987; 71: 645–6

15 Kolker A, Hetherington JJr *Becker-Schaffer's diagnosis and management of the glaucomas* 4th ed St Louis: Mosby, 1976 183.

16 Hitchings RA Glaucoma. In. Miller S, ed. *Clinical ophthalmology*. London: Butterworth, 1987, chapter 11: 304–20

17 Tomlinson A, Leighton DA Ocular dimensions in the heredity of angle closure glaucoma *Br J Ophthalmol* 1973; 57: 475–86

18 Rodrigues MM, Krachmer JH, Hackett J, Gaskins R, Halkias A. Fuchs' corneal dystrophy a clinicopathological study of the variation in corneal oedema. *Ophthalmology* 1986; 93: 789–96.

19 Krachmer JH, Purcell JJJr, Young CN, Bucher KD. Corneal endothelial dystrophy. A study of 64 families *Arch Ophthalmol* 1978; 96: 2036–9

20 Sorsby A. Biology of the eye as an optical system. In: Duane TD, ed. *Clinical ophthalmology*. Hagerstown: Harper and Row, 1984; 1: chapter 3.

21 Jay JL. Extracapsular lens extraction and posterior chamber intraocular lens insertion combined with trabeculectomy. *Br J Ophthalmol* 1985, 69: 487–90

British Journal of Ophthalmology, 1990, 74, 605–606

Effect of a β-blocker on altered body position: induced ocular hypertension

Dean A Smith, Graham E Trope

Department of Ophthalmology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
D A Smith
G E Trope

Correspondence to
Dr G E Trope, EN5-306,
Toronto General Hospital, 200
Elizabeth Street, Toronto,
Ontario, Canada M5G 2C4

Accepted for publication
3 May 1990

Abstract

The intraocular pressures (IOP) were measured in both eyes of 25 healthy volunteers in various body positions. One eye was pretreated with levobunolol 0·5% or placebo applied in a masked, randomised fashion, while the other served as control. IOP changes in response to levobunolol and to changes in position were significant ($p<0.0001$). However, pressure rises relative to position were not significantly different in eyes treated with drug vs placebo. Levobunolol did not alter relative changes in IOP from changes in body position. However, the overall lowering effect may offer some protection to patients with glaucoma.

Changes in body position have been shown to affect intraocular pressure (IOP).[1 2] Physiological changes include IOP increases of 1–4 mmHg in going from the sitting to the horizontal position, to IOP doubling on gravity inversion.[3] These pressure changes occur rapidly in both induction and reversal and are sustained in a given position.[2] In addition to IOP changes, gravity inversion has also been shown to cause transient changes in automated visual fields,[4] pattern reversal electroretinograms (ERG), and visually evoked potentials (VEP).[5]

The mechanism for IOP changes is thought to be due to decreased outflow secondary to increased episcleral venous pressure combined with vascular engorgement of the uvea.[2] Carlson *et al* have shown that aqueous flow does not notably change in response to altered body position.[6]

Exaggerated increases of IOP in the horizontal position have been shown to occur in patients with glaucoma,[7 8] particularly following trabeculectomy.[9] Anderson and Grant noted that eyes receiving miotics also showed an exaggerated response.[1] However, this may have been due to the underlying glaucomatous state.

To our knowledge the effect of antiglaucoma medications on postural changes in IOP has not been studied in a randomised and controlled fashion. For this study, we chose the nonspecific β-blocker levobunolol* as the test drug.

Materials and methods

Twenty-five healthy volunteers were enrolled after informed consent was obtained. The study was approved by the Ethics Review Board of the Toronto General Hospital.

General medical and ocular histories were obtained and a full eye examination was performed. The subjects were then randomly assigned to the right or left eye and in a double blind fashion to drug or placebo. IOP measurements were determined by Perkins tonometry.[10] The subjects were given one drop of levobunolol 0·5% or placebo. Then measurements were taken on both the treated and untreated eyes as follows: pretreatment sitting, two hours post-treatment sitting, horizontal, 30° head down, horizontal, and a final sitting. Pressures were taken within 10–15 seconds of assuming new positions and in most instances were an average of two readings. One week later the same IOP routine was performed with the alternative drop on the same eye.

An F test analysis of variance was performed on the IOP measurements to detect differences created by position, treatment, and order (drug→placebo versus placebo→drug).

Table 1 Elevations in intraocular pressure (mmHg) from the sitting position

	Horizontal	*30° Head down*
Placebo	1·6 (SD 0·4)	13·7 (SD 0·8)
Drug	1·2 (SD 0·4)	13·4 (SD 0·7)

Results

There were 25 subjects, 11 male and 14 female. The age range was 13–44 years, mean 28·2 years. Four had a family history of glaucoma. All the eyes were clinically normal. Levobunolol lowered the IOP by an average of 1·65 mmHg after two hours ($p<0.0001$). Table 1 demonstrates IOP elevations in the horizontal and 30° head down positions. It is noteworthy that the IOP rose 1·6 mmHg in the untreated group and 1·2 mmHg in the treated group in the horizontal

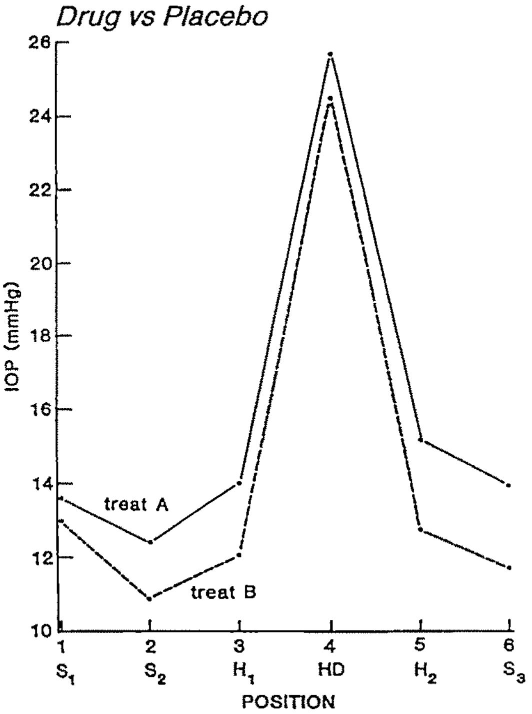


Figure 1 Positional IOP curves for drug (treat B) and placebo (treat A). S_1=pretreatment sitting. S_2=post-treatment sitting. H_1=initial horizontal. HD=head down at 30°. H_2=final horizontal. S_3=final sitting.

*The authors have no commercial or proprietary interest in this drug

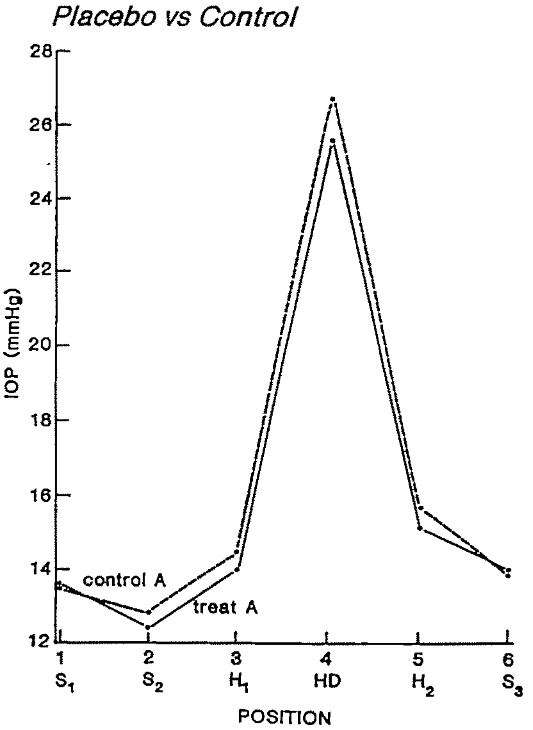


Figure 2 Positional IOP curves for placebo (treat A) and control (opposite eye). See key under Figure 1.

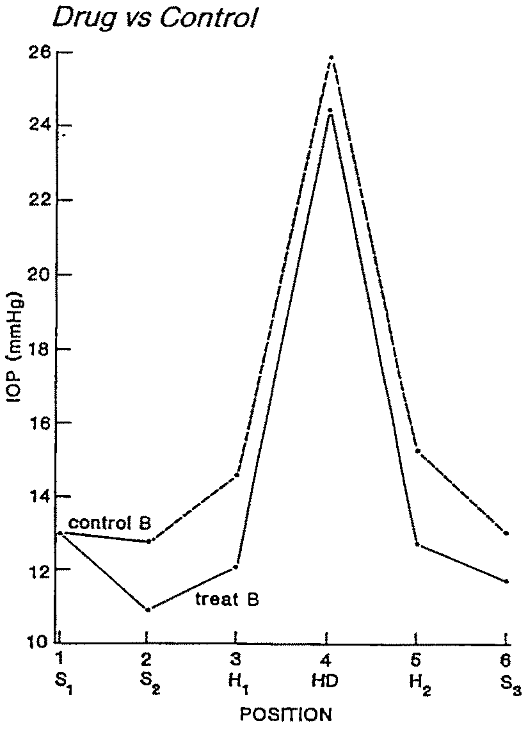


Figure 3 Positional IOP curves for drug (treat B) and control (opposite eye). See key under Figure 1.

position. Tilting the body 30° head down caused increases of 13·7 mmHg in the untreated group and 13·4 mmHg in the treated group. These results are also highly significant ($p<0.0001$).

The positional IOP curves for drug and placebo were parallel (Fig 1). This was also true of the control eyes (opposite eyes) for both placebo and drug (Figs 2 and 3). Levobunolol lowered the IOP in all positions but did not alter the *relative* IOP changes between positions.

It was interesting to note that in treated eyes the initial horizontal IOPs stayed below pretreatment sitting levels in comparison with both placebo and control.

Discussion

The results of this study confirm earlier reports that acute rises in IOP can be induced by changes in body position. The average rises of 1·4 and 13·6 mmHg in going from the sitting to the horizontal and 30° head down positions respectively are compatible with the 0·3 mmHg increase noted by Leonard *et al*[2] and the 16 mmHg increase noted by Weinreb *et al.*[3] In the latter study subjects were totally inverted, which explains the greater IOP effect.

Coakes and Brubaker have shown by fluorophotometric studies that the β-blocker timolol maleate decreases aqueous production[11] and that this is the most likely mechanism for its IOP reducing effect. We have shown that the β-blocker levobunolol has no effect on relative IOP changes with altered body position. Thus these changes appear to be insensitive to changes in aqueous production. This indirectly confirms the more recent work by Carlson and associates[6] which showed, again by aqueous fluorophotometry, that aqueous production was not significantly altered by posturally induced elevated IOP. Therefore the mechanism for elevated IOP in the horizontal and head down positions must be due to reduced outflow, as proposed by Leonard *et al.*[2]

The reduction in IOP caused by levobunolol was enough to prevent the horizontal IOP from reaching pretreatment sitting levels. This may have important therapeutic implications for patients with glaucoma, particularly those giving an exaggerated postural IOP response.

In future studies the effect of various antiglaucoma medications on the postural IOP response in normal and glaucoma patients should be studied.

The authors thank Allergan Inc and Merck Frosst Canada Inc for contributing funds for this paper We also thank Professor M Chipman, Department of Biostatistics and Preventive Medicine, University of Toronto, for her assistance with the statistical analysis. Finally, we thank Dr R R Nishimura for her assistance with the research and preparation of the manuscript.

1 Anderson DR, Grant WM. The influence of position on intraocular pressure *Invest Ophthalmol Vis Sci* 1973; 12: 204–12
2 Leonard TJK, Kerr Muir MG, Kirkby GR, Hitchings RA. Ocular hypertension and posture. *Br J Ophthalmol* 1983, 67: 362–6.
3 Weinreb RN, Cook J, Friberg TR. Effect of inverted body position on intraocular pressure. *Am J Ophthalmol* 1984, 98: 784–7.
4 Sanborn GE, Friberg TR, Allen R. Optic nerve dysfunction during gravity inversion – visual field abnormalities *Arch Ophthalmol* 1987; 105: 774–6
5 Linder BJ, Trick GL, Wolf ML Altering body position affects intraocular pressure and visual function. *Invest Ophthalmol Vis Sci* 1988, 29: 1492–7.
6 Carlson KH, McLaren JW, Topper JE, Brubaker RF. Effect of body position on intraocular pressure and aqueous flow. *Invest Ophthalmol Vis Sci* 1987; 28: 1346–52.
7 Wuthrich UW. Postural change and intraocular pressure in glaucomatous eyes. *Br J Ophthalmol* 1976; 60: 111–4.
8 Tsukahara S, Sasaki T Postural change of IOP in normal persons and in patients with primary wide open-angle glaucoma and low-tension glaucoma. *Br J Ophthalmol* 1984, 68: 389–92
9 Parsley J, Powell RG, Keightley SJ, Elkington AR. Postural response of intraocular pressure in chronic open-angle glaucoma following trabeculectomy. *Br J Ophthalmol* 1987, 71: 494–6.
10 Perkins ES Hand-held applanation tonometer *Br J Ophthalmol* 1965, 49: 591–3.
11 Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure. *Arch Ophthalmol* 1978; 96: 2045–8

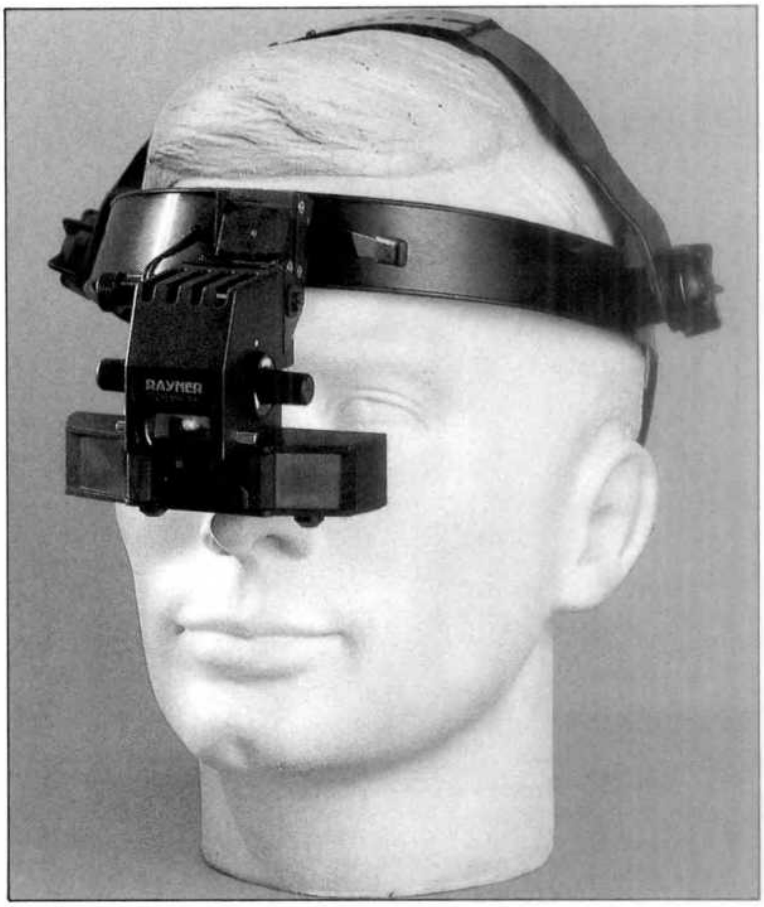
RAYNER present their new

'Professional' Indirect Ophthalmoscope

Rayner Optical have harnessed the latest developments in engineering and technology to bring you a remarkable new Indirect Ophthalmoscope – The Professional – A totally new indirect with many unique features embodied in the most compact and practical form.

Special Features:

- ☐ Blue Hazard filter protection
- ☐ Small Pupil facility
- ☐ Unique 'Park' mechanism
- ☐ Two Second Observer mirrors that can be swung in individually
- ☐ Cobalt Blue filter
- ☐ Red Free filter
- ☐ Charging System
- ☐ Full Range P.D. adjustment
- ☐ Lightness and comfort
- ☐ Heat Protection for patient and practitioner



The Blue Hazard filter gives you patient protection from those harmful wavelengths in the visible blue area. All pupil facility; three light patch sizes are available. A unique "park" facility which allows for the ophthalmoscope to be moved out of the line of vision when not being used

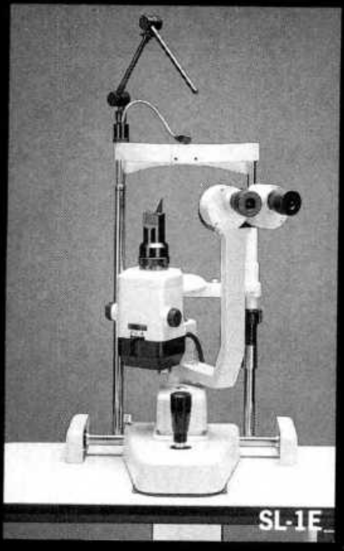
The second observer mirrors can be simply pivoted into position when required.
Filter selection – cobalt blue for fluorescence angioscopy AND Red-free for increased contrast when viewing retinal blood vessels, haemorrhages, etc.

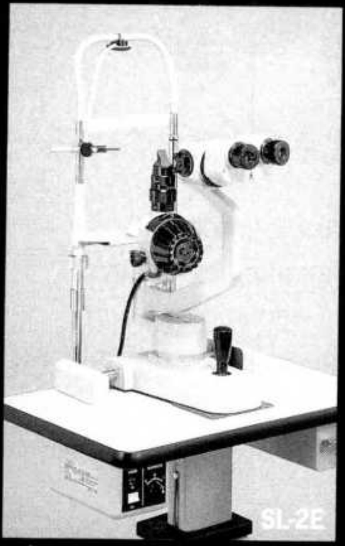
A compact power pack with combined holder/charging well for a portable battery unit.
P.D. adjustment range 52-74mm. A fully adjustable headband, designed for prolonged wear and comfort. The optical system has been designed to give the optimum viewing and illumination angle. A powerful 6V low halogen prefocused lamp is used.

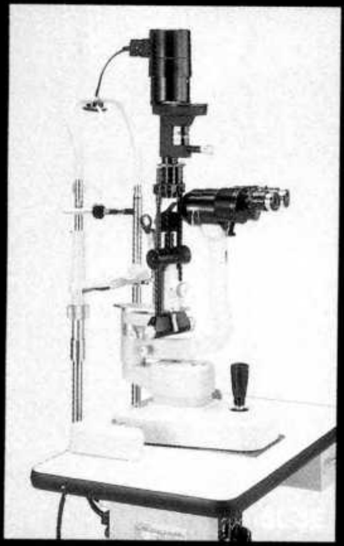
For full details about our range and for our new Catalogue, please contact the Product Information Department

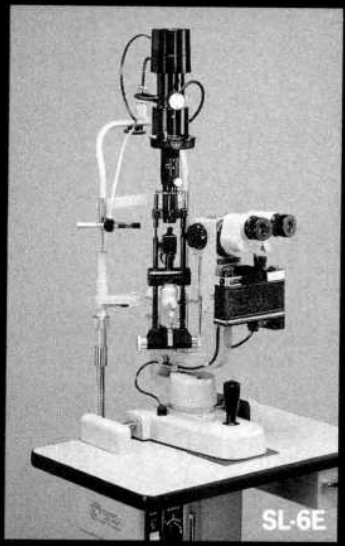
The Rayner Optical Company Limited

17 Lorna Road, Hove, East Sussex BN3 3EP, England Tel: 0273-778331 Fax: 0273-720214









SL-1E
- 14mm slit illumination
- Omni directional joystick
- Variable magnification capability
- Built-in filters
- Halogen illumination

SL-3E
- Omni directional joystick
- Two fixation targets
- Convenient, lever-controlled magnification change
- Slit beam inclination
- Four built-in filters
- Infinitely adjustable slit width and length
- Pachometer attachment

SL-2E
- Convergent binocular tubes enhance the examination
- Omni directional joystick
- Three-position magnification
- Infinitely adjustable slit width and length
- Built-in filters
- 35mm photographic attachment

SL-6E
- Convergent binocular tubes for unprecedented viewing
- Omni directional joystick
- Five-position magnification
- Four built-in filters
- 35mm photographic attachments
- Polaroid attachment model PA-8S
- Video attachment
- Non-contact specular attachment
- Pachometer attachment
- Observation tube

In keeping with our philosophy of supplying only top quality equipment, Keeler are now the exclusive distributors for TOPCON.

The full range of Topcon slit lamps allows the practitioner to choose exactly the right instrument for his particular needs.

Within the range, Topcon now offers high magnification versions of their most popular slit lamps. These are illustrated opposite, and the details listed below.

If a permanent record is required, then this is achievable with photographic attachments which allow the use of 35mm, Polaroid or, in the case of the SL-6E, video recording.

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

ONDON CENTRE
eeler Martin and Tomkins, 38 Margaret Street,
Cavendish Square, London W1A 4NS
Telephone: 01-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
elephone: (0236) 721214 Fax: (0236) 721231

British Journal of Ophthalmology, 1990, 74, 607–609

A functional vagotomy induced by unilateral forced right nostril breathing decreases intraocular pressure in open and closed angle glaucoma

Joshua Backon, Nelson Matamoros, Manuel Ramirez, Rodrigo M Sanchez, Jaime Ferrer, Alberto Brown, Uriel Ticho

Mount Pleasant Hospital Addiction Studies Foundation, PO Box 16336, Jerusalem, Israel
J Backon

Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel
N Matamoros
M Ramirez
R M Sanchez
J Ferrer
A Brown
U Ticho

Correspondence to
Dr J Backon

Accepted for publication
11 May 1990

Abstract

There is evidence of the central regulation of intraocular pressure, and it has been suggested that vagal tone might be increased in glaucoma simplex. The nasal cycle, the simultaneous congestion-decongestion response in the nasal cavities, reflects the dynamic lateralisation of the autonomic nervous system. Since this lateralisation presents with sympathetic activity induced by left brain hemisphere stimulation and parasympathetic activity induced by right hemisphere stimulation, it was subsequently demonstrated that forced unilateral nostril breathing induces selective contralateral hemispheric stimulation as measured by relative increases in the electroencephalographic amplitude in the contralateral hemisphere as well as alternating lateralisation of plasma catecholamines. Using this functional vagotomy, we report that left hemispheric stimulation by 20 minutes of forced unilateral right nostril breathing led to a significant bilateral decrease of 4·6 mmHg (25%) in intraocular pressure in 46 patients with open and closed angle glaucoma. However, it significantly increased the IOP in three patients with neovascular, one with juvenile onset, and one with closed angle glaucoma.

Adrenergic influences on aqueous humour dynamics and intraocular pressure are well documented,[1-3] and it has been suggested that vagal tone may be raised in glaucoma simplex.[4 5]

The nasal cycle, the simultaneous congestion-decongestion response in the nasal cavities, reflects the dynamic lateralisation of the autonomic nervous system.[6] Since this lateralisation presents with sympathetic activity induced by left brain hemisphere stimulation and parasympathetic activity induced by right hemisphere stimulation, it was subsequently demonstrated that forced unilateral nostril breathing induces selective contralateral hemispheric stimulation as measured by relative increases in the electroencephalographic (EEG) amplitude in the contralateral hemisphere[7] as well as alternating lateralisation of plasma catecholamines.[8] We have used forced unilateral nostril breathing as a functional vagotomy/sympathectomy in the investigation of autonomic parameters such as T and QRS-T axis vectors in the electrocardiogram, stroke volume, parotid salivary flow rate, and parotid salivary immunoglobulins, glycaemic homoeostasis,[9] pupillary dilation, hippus and pupil cycle time, transcutaneously measured blood gases, blink rates,[10] pulse wave velocity, and vagal tone as measured by spectral analysis of R-R intervals of the electrocardiogram. Using this functional vagotomy/sympathectomy in an experimental design, we recently reported the novel finding that right hemispheric activation via forced unilateral left nostril breathing increased the IOP by an average of 4·5%, whereas left hemispheric stimulation via forced unilateral right nostril breathing led to a significant (25%) decrease in IOP.[11] We subsequently used a functional vagotomy via forced unilateral right nostril breathing to lower the IOP by an average of 4 mmHg in 68 normal volunteers.[12] We now report the results of our technique in glaucoma patients.

Material and methods

We investigated the effect of forced unilateral right nostril breathing on the IOP in 51 patients with diagnosed glaucoma (31 males, 20 females, aged 15–78). There were 33 subjects with open angle, 14 with closed angle including two with acute closed angle, three with neovascular, and one with juvenile glaucoma. After baseline testing of the IOP each subject underwent 20 minutes of forced unilateral right nostril breathing, with the contralateral nostril stuffed with cotton packing. To guard against observer bias the junior registrar who did the applanation tonometry was not told why the subject had his nostril stuffed. All patients were under standard pharmacological treatment, and some had even undergone surgical intervention.

Both parametric and non-parametric tests were used to determine statistical significance. All statistical results report 2-tailed values, except for the binomial test, where 1-tailed results are reported.

Results

As ascertained by applanation tonometry, we found a significant ($p<0.0001$) reduction of IOP with forced unilateral right nostril breathing even after pharmacotherapy and/or surgical intervention. Apart from the findings in the 'outliers' (the three with neovascular glaucoma, the one with juvenile, and the one with closed angle) the IOP was bilaterally lowered an average of 4·6 mmHg from baseline. This decrease was 5·26 mmHg in the right eye and 4·24 mmHg in the left. Contraindications were not found and no side effects were reported. Higher baseline values of IOP resulted in a significantly greater effect of treatment. The baseline IOP was arbitrarily dichotomised as 20 mmHg or lower and

21 mmHg or higher. When the baseline IOP of the right eyes was greater than 21 mmHg, the median difference after treatment was 8 mmHg (32% difference), whereas if the baseline was lower than 21 mmHg the median difference was only 4 mmHg (23% difference). When the baseline IOP of the left eyes was greater than 21 mmHg the median difference after treatment was 6 mmHg (27·3% difference), whereas if lower than 21 mmHg the median difference was only 3·5 mmHg (19·5% difference). The 'outliers' were included in these calculations. Overall, the average percentage decrease in IOP was 27% in the right eyes and 22·5% in the left.

Omega-squared (ω^2) is one of the most frequently applied methods in estimating the proportion of the dependent variable accounted for by an independent variable, and it is used to confirm the strength of association between variables in a population.[13] Here ω^2 was 21·5% for the right eyes and 17·2% for the left. The 'outliers' were included in these calculations.

Reliability in repeated applanation tonometry was investigated in 1972. Repeated Goldmann applanation tonometry every minute for 5 minutes in normal subjects gave a direct pressure reduction of approximately 2·62 mmHg in 5 minutes, whereas applanation tonometry carried out twice in a 5-minute period reduced the IOP only by 0·4 mmHg.[14] Since the normal mean IOP is 15·4 mmHg (SD 2·5), this gives a reliability of at least 83% (2·62/15·4). The percentage change in our investigation was on average much higher than 17%. In order to verify that the intervention of forced unilateral nostril breathing was in fact the factor inducing the change in IOP, we measured the IOP twice in a 15-minute period in another group of 12 patients with open angle glaucoma. Interestingly, the mean change in IOP in both left and right eyes was 0·417 mmHg. The percentage change was 5·1% in the right eyes and 2·5% in the left. Both measurements were highly correlated (Pearson r=0·99), and neither parametric nor non-parametric testing revealed any statistically significant differences between measurements.

Table 1 Effect of 20 min of forced unilateral right nostril breathing on the IOP (all groups combined)

		Right eye	*Left eye*
Baseline			
	Mean	20 15	18 71
	Median	19·00	18 00
	SD	6·13	4·03
After 20 minutes of FURNB*			
	Mean	16 31	15 64
	Median	14·00	15 00
	SD	7 04	6·43

n=51.
One-way ANOVA both eyes p=<0·00048
One-way ANOVA right eye p=<0 0040.
One-way ANOVA: left eye p=<0·0049.
Signed rank test p=<0 0000034
Binomial test at 50% p=<0·000001, at 33% p=<0·000001
Pitman randomisation test p=<0·00001
*Forced unilateral right nostril breathing.

Table 2 Effect of 20 minutes of forced unilateral right nostril breathing on the IOP in glaucoma subcategories.

	Mean decrease in IOP (mmHg) after intervention (SD in parentheses)[range in brackets]			*Mean percentage decrease after intervention (SD in parentheses) [range in brackets]*		
	Right eye	*Left eye*	*Average of both eyes*	*Right eye*	*Left eye*	*Average of both eyes*
Open angle n=33	5·3 (2·0) [2–11] p<0·000001	4·6 (2 4) [1–12] p<0·000001	4·95	29 [10–75]	24·2 [6–46]	26 6
Closed angle n=12 (including outlier)	3·9 (2 9) [−2–8] p<0·0007	2 75 (2·8) [−4–6] p<0 006	3·32	18 3 [−13–33]	14 2 [−29–35]	16 25
Close angle n=11 (without outlier)	4 45 (2·4) [0–8] p<0 0001	3·36 (2·0) [0–6] p<0 0002	3·90	21 [0–33]	18 [0–35]	19 5
Acute closed angle n=2	9 (4·2) [6–12]	3 5 (2·1) [2–5]	6 25	21 5 [17–26]	19·5 [11–28]	20·5
Neovascular n=3	+10·67 (5 0) [+6–+16]	+7 (7·9) [+1–+16]	+8·84	+51 [+31–+89]	+25 [+6–+40]	+38
Juvenile n=1	+12	+14		+86	+117	

+Signifies increase

However, the IOP was significantly increased after forced unilateral right nostril breathing in the three subjects with neovascular glaucoma, the one subject with juvenile glaucoma, and one subject with closed angle glaucoma. The IOP decreased in all other patients, including the subject with acute closed angle glaucoma.

Statistical analysis by both parametric and non-parametric tests are indicated in Table 1 (all groups combined). Breakdown by category appears in Table 2 along with an appropriate statistical analysis.

Discussion

This study shows the fascinating autonomic regulation of intraocular pressure by forced unilateral nostril breathing. Such regulation has been demonstrated in an experimental study,[11] in eyes with normal pressure,[12] and now in patients with glaucoma. The decrease in values of IOP (4·6 mmHg) by forced unilateral right nostril breathing in the glaucoma patients was similar to that found in the eyes of normal pressure. Pharmacological intervention (pilocarpine, acetazolamide) in glaucoma patients, however, is known to reduce the IOP by 1 torr (133 N m^{-2}) over that lowered by pharmacological intervention in eyes of normal pressure. We can offer no explanation why the forced breathing technique lowers the IOP to the same level in both normal people and glaucoma patients. The effect of forced unilateral right nostril breathing is almost immediate, and it induces a reduction in IOP of up to 30–35%, as compared with pharmacotherapy, which takes effect over a period of 20–30 minutes and induces a change in IOP in the range of 15–35%.[15–17] What remains to be investigated is the exclusive use of the technique without the use of pharmacotherapy.

Keeping in mind the role of innervation to the ciliary body and outflow channels, we have not yet explored whether the technique inhibits the production and inflow of aqueous, or whether it activates the outflow pathways.

It is unclear why the technique greatly increased the IOP in the patients with juvenile and neovascular glaucoma. It is possible that forced unilateral right nostril breathing may not be effective in lowering the IOP in cases of juvenile and neovascular glaucoma because of the presence of major impediments to aqueous outflow.

Although the technique has a short-term, approximately 2–3-hour effect and cannot be offered as a clinical intervention, it may shed light on factors affecting chronic nasal resistance such as the effect of lateral recumbency,[18–28] the presence of septal deviation and of nasal polyps. One of us (NM) has found some preliminary evidence of an increased incidence of nasal polyps in the right turbinate of glaucoma patients. The skin-pressure vegetative reflex,[18] which affects nasal resistance, has been found to regulate parameters mediated by the autonomic nervous system. These factors need to be further studied in glaucoma patients.

1 Greaves DP, Perkins ES. Influence of the sympathetic nervous system on the intraocular pressure and vascular circulation of the eye. *Br J Ophthalmol* 1952, 36: 258–64.
2 Langham ME, Rosenthal AR. Role of the cervical sympathetic nerve in regulating intraocular pressure and circulation *Am J Physiol* 1966; 210: 786–94.
3 Belmonte C, Bartels SP, Liu JHK, Neufeld AH. Effects of stimulation of the ocular sympathetic nerves on IOP and aqueous humor flow. *Invest Ophthalmol Vis Sci* 1987; 28: 1649–54.
4 Innemmee HC, van Zwieten PA The central nervous influence of drugs on intraocular pressure. *Rev Pure Appl Pharmacol Sci* 1980; 1: 107–65
5 Waitzman MB Hypothalamus and ocular pressure. *Surv Ophthalmol* 1971; 16: 1–23.
6 Werntz DA, Bickford RG, Bloom FE, Shannahoff-Khalsa DS. Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function. *Hum Neurobiol* 1983; 2: 39–43.
7 Werntz DA, Bickford RG, Shannahoff-Khalsa DS. Selective hemispheric stimulation by unilateral forced nostril breathing. *Hum Neurobiol* 1987; 6: 165–71.
8 Kennedy B, Ziegler MG, Shannahoff-Khalsa D Alternating lateralization of plasma catecholamines and nasal patency in humans *Life Sci* 1986; 38: 1203–14.
9 Backon J, Kullok S Changes in blood glucose levels induced by differential forced unilateral nostril breathing, a technique which affects both brain hemisphericity and autonomic activity. *Med Sci Res* 1988, 16: 1197–9.
10 Backon J, Kullok S. Effect of forced unilateral nostril breathing on blink rates: relevance to hemispheric lateralization of dopamine. *Int J Neurosci* 1989; 46: 53–9
11 Backon J, Matamoros N, Ticho U. Changes in intraocular pressure induced by differential forced unilateral nostril breathing; a technique that affects both brain hemisphericity and autonomic activity: a pilot study *Graefes Arch Clin Exp Ophthalmol* 1989; 227: 575–7.
12 Matamoros N, Backon J, Ticho U The effect of differential brain hemisphericity, induced by forced unilateral nostril breathing, on regulation of intraocular pressure In. de Oliveira LNF, ed *Ophthalmology today*. Excerpta Medica International Congress Series 1988, 803: 679–80
13 Torabi MR. How to estimate practical significance in health education research. *J Sch Health* 1986, 56: 232–4
14 Wilke K. Effects of repeated tonometry: genuine and sham measurements. *Acta Ophthalmol (KGh)* 1972; 50: 574–82.
15 Hepler RS, Frankl IM. Marihuana smoking and intraocular pressure. *J AMA* 1971; 217: 1392.
16 Makabe R. Ophthalmologische Untersuchungen mit dichlorphenyl-aminoimidazolin. *Dtsch Med Wochenschr* 1966; 91: 1686–8.
17 Zimmerman TJ, Kaufman HE. Timolol, a beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; 95: 601–4.
18 Takagi K, Kobayasi S Skin pressure-vegetative reflex. *Acta Medica Biol* 1955; 4: 3–57.
19 Cole P, Haight JSJ. Posture and the nasal cycle *Ann Otol Rhinol Laryngol* 1986, 95: 233–7.
20 Davies AM, Eccles R. Reciprocal changes in nasal resistance to airflow caused by pressure applied to the axilla. *Acta Otolaryngol (Stockh)* 1985; 99: 154–9.
21 Haight JSJ, Cole P. Topographical anatomy of pressure points that alter nasal resistance *J Otolaryngol* 1986, suppl 16 14–20.
22 Kosaka M, Takagi K, Koyama M. Reflex inhibition of cold shivering by pressure in the skin and the histological investigation of its afferent spinal pathway *Experientia* 1967; 23: 453–5.
23 Kumazawa T 'Deactivation' of the rabbit's brain by pressure application to the skin *Electroencephalogr Clin Neurophysiol* 1963, 15: 660–71.
24 Nakayama T. Behaviour of cervical muscles in labyrinthine and skin-pressure reflexes *Jpn J Physiol* 1957, 7: 99–112
25 Ogawa T, Asayama M, Ito M, Yoshida K. Significance of skin pressure in body heat balance *Jpn J Physiol* 1979; 29: 805–16.
26 Rao S, Potdar A Nasal airflow with body in various positions. *J Appl Physiol* 1970; 28: 162–5.
27 Singh V. Thoracic pressure and nasal patency. *J Appl Physiol* 1987, 62: 91–4.
28 Takagi K Uber den Einfluss des mechanischen Hautdruckes auf die vegetativen Funktionen *Acta Neurovegetativa* 1957, 16: 439–47.

British Journal of Ophthalmology, 1990, 74, 610–614

Choroidal lesions in patients with AIDS

Marc A Rosenblatt, Carol Cunningham, Steven Teich, Alan H Friedman

Abstract

Seven cases of bilateral, scattered, yellow-white choroidal lesions have been seen in AIDS patients since January 1988. One resulted from presumed extension of cryptococcal meningitis into the optic nerve and choroid. All the remaining six patients had pneumocystis pneumonia at some time during the course of the disease and were receiving aerosolised pentamidine therapy. None died quickly of disseminated *Pneumocystis carinii* infection, unlike previously reported patients. Mycobacterial infection was also present in five of these six patients. The differential diagnosis of this entity in AIDS patients is discussed.

Scattered choroidal yellow-white lesions in AIDS patients have recently been described as a marker for disseminated and rapidly fatal *Pneumocystis carinii* infection.[1] We present a series of seven cases with similar appearances but varied outcomes. Possible alternative aetiologies are discussed.

Case reports

CASE 1

A 31-year-old homosexual male with AIDS had four previous episodes of *Pneumocystis carinii* pneumonia and one of cytomegalovirus (CMV) pneumonia. *Mycobacterium avium intracellulare* infection had been noted on endobronchial biopsy. Medications included isoniazid, rifampicin, ganciclovir, and aerosolised pentamidine. During recurrence of pneumonia, which was without visual symptoms and with normal acuity, examination with dilated pupils revealed bilateral, flat, yellow-white choroidal lesions through all quadrants, varying in size from 0·25 to 2 disc diameters. Rapid plasma reagin, toxoplasmosis immunofluorescence antibody test, and serological tests for histoplasmosis, coccidioidomycosis, and cryptococcus were negative. After three weeks of intravenous pentamidine and a reinduction course of ganciclovir the pneumonia cleared. After two months the choroidal lesions became more discrete and orange, with overlying pigment proliferation. He died of staphylococcal septicaemia 11 months later without necropsy.

CASE 2

A 32-year-old homosexual male with AIDS was found to have normal acuity and approximately 20 choroidal lesions in each eye while in hospital in June 1988 for cryptococcal meningitis with bone marrow involvement and increased intracranial pressure. Despite treatment with intravenous amphotericin, palsies of cranial nerves III, V, VI, and VII developed. The optic disc was swollen, with dilated retinal venules and peripapillary haemorrhages.

Computerised tomography revealed enlarged optic nerves. Despite treatment with flucytosine and intravenous dexamethasone, vision deteriorated to finger counting in both eyes after one month. An electroretinogram (ERG) was normal, but visually evoked potential (VEP) was unrecordable. Fluorescein angiography revealed diffuse disc leakage and hypofluorescence corresponding to the choroidal lesions. Visual loss was thought to be due to cryptococcal invasion of the optic nerves.

CASE 3

A 28-year-old homosexual male with AIDS had multiple episodes of *P carinii* pneumonia, after which he received aerosolised pentamidine. CMV retinitis of the right eye treated with ganciclovir progressed to a retinal detachment. Isoniazid, rifampicin, and ethambutol were prescribed for bone marrow granulomas. Subretinal creamy yellow-white lesions appeared about the macula in the left eye. Over two weeks similar lesions appeared under the bullous detachment in the right eye, and new lesions appeared in the left eye. Vision remained 20/20 in the left eye. Fever developed. Serological testing for rapid plasma reagin, toxoplasmosis, cryptococcus, coccidiomycosis titres, adenovirus titres, and Epstein-Barr virus titres were negative. A gallium scan showed increased uptake in the mediastinum and retroperitoneal lymph nodes. Intravenous pentamidine was begun for presumed disseminated *P carinii* infection. The choroidal lesions become more discrete and orange, with pigment proliferation at their edges. The patient returned home on oral dapsone prophylaxis for *P carinii* pneumonia (PCP), and one month later his local ophthalmologist noted no evidence of choroidal lesions in either eye. His visual acuity was light perception OD and 20/20 OS.

CASE 4

A 37-year-old intravenous drug user with AIDS, maintained on aerosolised pentamidine after five bouts of *P carinii* pneumonia, had 20/40 vision OD while in the hospital for bronchoscopy-proven pneumocystis pneumonia. Amsler grid testing revealed a large paracentral scotoma OD. Examination under dilated pupils showed a five-disc diameter, flat, grey-yellow choroidal lesion subfoveally with a brighter area as its nasal edge, suggesting more acute inflammation. Ten to 15 smaller choroidal lesions were scattered outside the posterior pole. In the left eye there were at least 20 similar choroidal lesions. The pneumonia improved on trimetrexate and the lesions became

Department of Ophthalmology, Mt Sinai School of Medicine, New York
M A Rosenblatt
S Teich
A H Friedman

Department of Ophthalmology, New York University School of Medicine, New York
C Cunningham

Correspondence to:
M A Rosenblatt, MD, 9 East 75th Street, New York, NY 10021, USA

Accepted for publication 11 May 1990

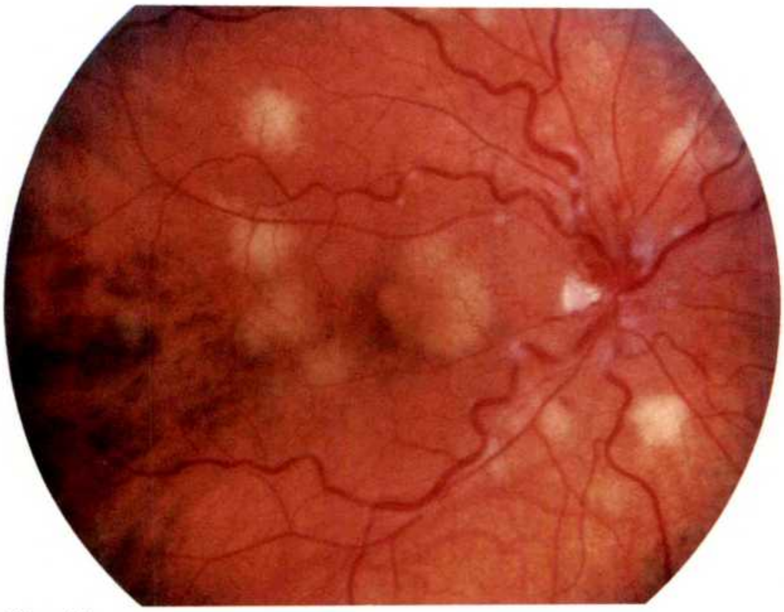


Figure 1A

Figure 1 Case 6. A: Right eye: Scattered lesions with one under the fovea and flame haemorrhages at the disc margin with several cotton-wool spots and haemorrhages. Visual acuity 20/80. B: Left eye: similar retinal lesions on presentation. C: Fluorescein angiogram right eye, early arteriolar phase showing hypofluorescence of lesions. D: Fluorescein angiogram right eye, hyperfluorescence later in sequence.

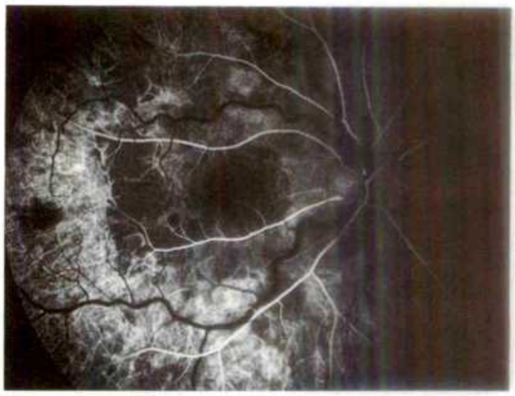


Figure 1C

more distinct. Serological testing for syphilis (VDRL), cryptococcal antigen, and toxoplasmosis gave negative results. A diagnosis of presumed disseminated *P carinii* infection was made and the patient put on prophylactic therapy with oral dapsone. A splenectomy three months later for idiopathic thrombocytic purpura revealed both *P carinii* and acid-fast bacteria. Isoniazid and ethambutol were added to the treatment. A year later, during the seventh admission to hospital for *P carinii* pneumonia, acuity and Amsler grid results had returned to normal and the choroidal lesions had become deep orange.

CASE 5

A 42-year-old AIDS patient had three recurrences of PCP in two years; he was taking rifampicin and isoniazid for *Mycobacterium avium intracellulare* infection, acyclovir for herpes simplex, aerosolised pentamidine for PCP, and azathioprine. CMV retinitis was found in the left eye, reducing vision to 20/400. After treatment with ganciclovir for three months his acuity was unchanged, but he developed grey-yellow lesions throughout the right fundus at the level of the retinal pigment epithelium. Similar lesions were seen in the non-atrophic areas of the left fundus. Fluorescein angiography revealed early blockage and late staining of the lesions.

CASE 6

A 37-year-old male with AIDS was admitted to hospital in September 1988 for bilateral pleural effusions after eight months of aerosolised pentamidine. His visual acuity was 20/20 OU. Examination under dilated pupils revealed round and oval yellow-white choroidal lesions 0·5 to 2 disc diameters scattered in the posterior pole with one underlying the fovea OD. There were flame haemorrhages on and near the disc OD (Figs 1A, B). Fluorescein angiography revealed blockage early and late staining of the lesions (Figs 1C, D). A pleural tap revealed acid-fast bacilli; the patient's vision declined to 20/80 in the right eye. Isoniazid and rifampicin were begun as well as intravenous pentamidine. Two months later the visual acuity returned to 20/20 OD. Cultures grew *Mycobacterium avium intracellulare* from the pleural fluid, but cerebrospinal fluid (CSF) cultures were negative. By January 1989, four months after the initial examination, the lesions had totally resolved.

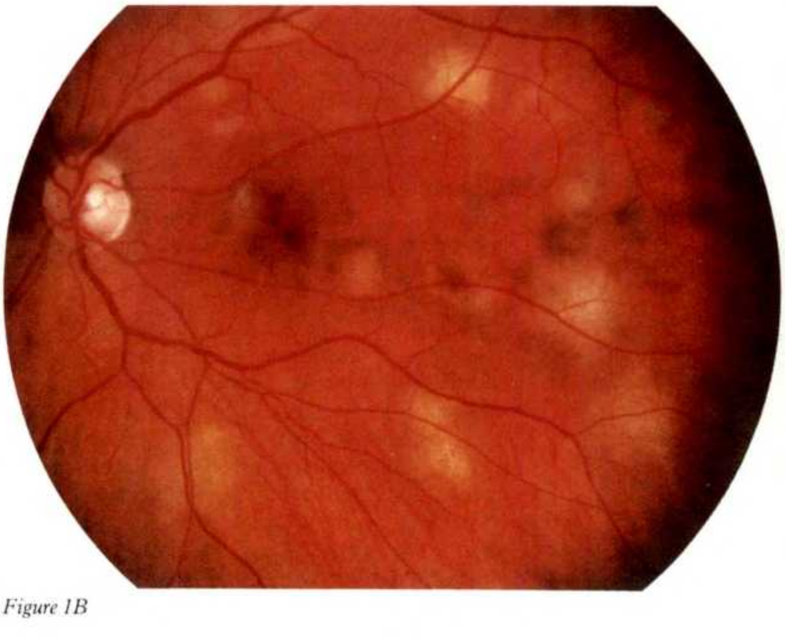


Figure 1B

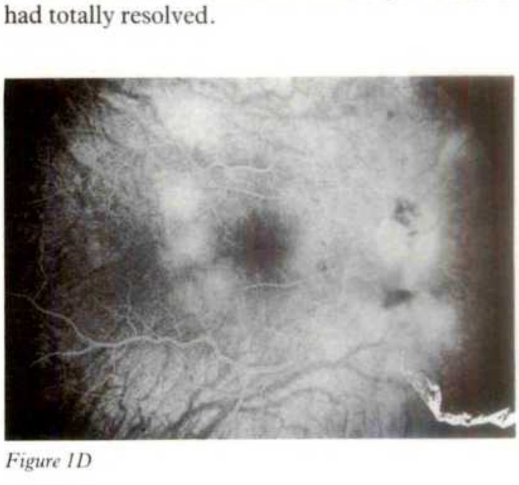


Figure 1D

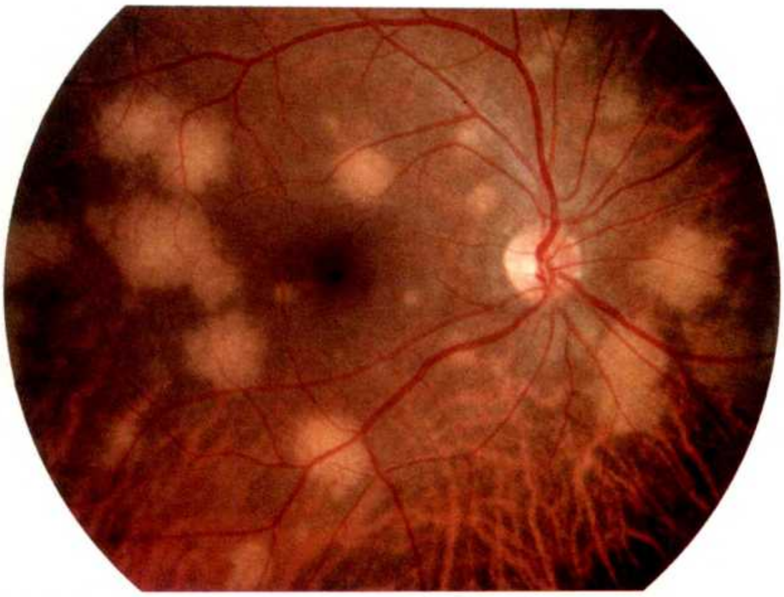


Figure 2A

Figure 2 Case 7: A: Right eye: deep yellow lesions on presentation. B: Left eye: subfoveal lesions with 20/20 visual acuity. C: Midphase fluorescein angiogram right eye, hyperfluorescence of lesions.

CASE 7

A 40-year-old AIDS patient had pneumocystis pneumonia three times treated with co-trimoxazole, intravenous pentamidine, and maintenance aerosolised pentamidine. On routine screening we found 20/20 vision OU and numerous grouped, yellow, deep round lesions in both eyes scattered about the posterior pole, some coalescing into larger oval lesions (Figs 2A, B). One lesion was directly subfoveal in the left eye. Fluorescein angiography revealed early blockage and late leakage (Fig 2C). Rapid plasma reagin, haemagglutination assay test for syphilis, and CMV titres were negative. The CSF was normal, with negative results to cryptococcal antigen and VDRL tests. The patient was anergic to skin testing. Vision remained stable, but the patient developed unexplained fevers.

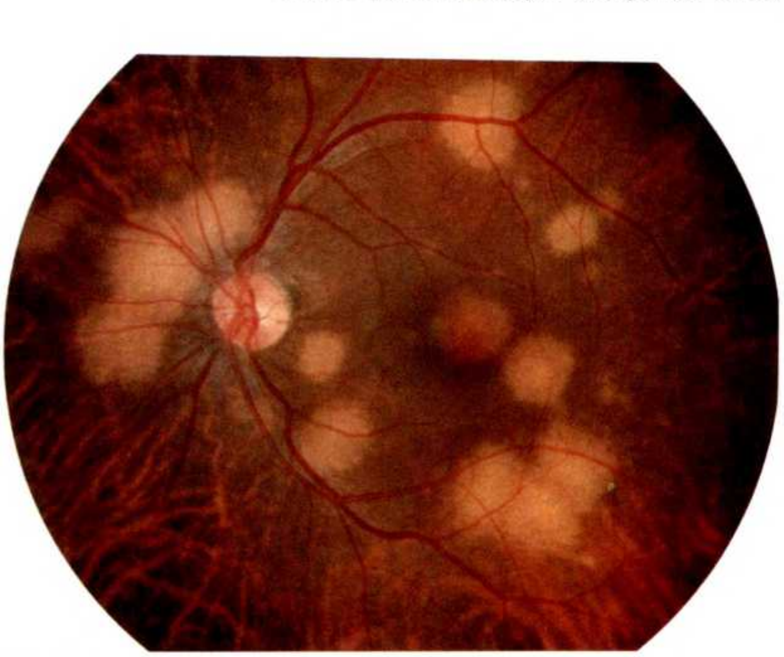


Figure 2B

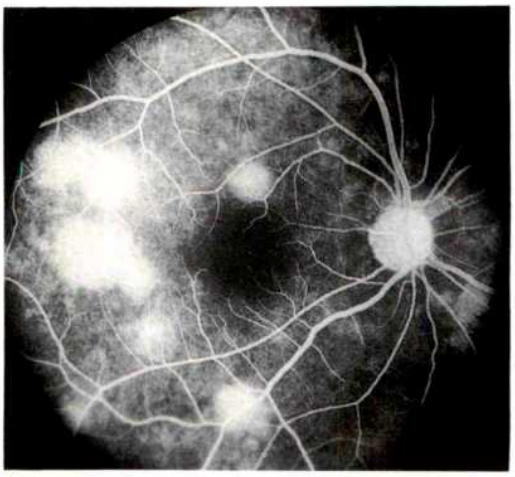


Figure 2C

Retroperitoneal adenopathy on CT scan and heterogeneous liver lesions on ultrasound prompted biopsy; the specimen was positive for acid-fast bacilli. Bone marrow aspirate was hypocellular, and acid-fast bacilli were not seen. Treatment was begun with isoniazid, rifampicin, pyrazinamide, and streptomycin. Six months after the initial findings, the visual acuity was stable and the lesions were fading.

Discussion

Choroidal lesions have occasionally been reported in AIDS patients. Macher *et al* described the histopathology of a case of yellow choroidal lesions secondary to *P carinii* infection.[2] More recently Rao *et al* reported three cases of yellow-white choroidal plaques which, on necropsy, revealed trophozoites of *P carinii*.[1] Visual acuity was decreased in one eye from accompanying CMV retinitis and reported as 20/30 and 20/60 in two other eyes. All the patients had received aerosolised pentamidine prophylaxis for *P carinii* pneumonia and all died within three weeks of discovery of the retinal lesions. The authors concluded that such fundus findings allow a presumptive diagnosis of disseminated *P carinii* disease and warrant agressive chemotherapy. Freeman *et al* described an AIDS patient, also on aerosolised pentamidine, with similar bilateral choroidal lesions which enlarged over a four-month period, found on transscleral choroidal biopsy to be due to *P carinii*.[3]

We examined seven patients with AIDS who also had bilateral yellow-white choroidal lesions. All were first noted after January 1988. As Rao *et al*[1] noted, the increasing discovery of these lesions may relate to increased survival, new therapies, or a change in microbial virulence. Only two patients were symptomatic at diagnosis (cases 4 and 6). Six of the seven patients (all but case 2) had had multiple pneumocystis infections and had been treated with aerosolised pentamidine. Such treatment produces low blood drug levels which may allow dissemination of *P carinii*.[4] Six patients also had *Mycobacterium avium* complex infections diagnosed from specimens of liver, blood, bone marrow, or pleural fluid. One patient (case 2) had cryptococcal meningitis with optic nerve involvement and died, blind, in four months. Another patient died after 15 months, without necropsy. In three patients (cases 3, 4, and 6) the lesions disappeared in three to six months during systemic treatment for PCP with intravenous trimetrexate or pentamidine followed by oral dapsone. The lesions remained unchanged in two of the patients after three to six months of follow-up. All our patients except number 2 are thought to represent cases of choroiditis due to disseminated *P carinii* infection. *P carinii* was demonstrated histologically in the spleen of patient 4. The clinical appearance of our cases is identical to that of the four previously reported cases.

Interestingly, these six patients also had disseminated mycobacterial infection, an entity whose frequent bacteraemias might account for seeding of the vascular choroid.[5,6] Little local tissue destruction and inflammation are associated with *M avium* infection, a fact compatible with normal acuity despite subfoveal lesions.[7,8] *M avium* has been cultured from one retina and choroid of an AIDS patient by Pepose *et al;* choroidal granulomas were found in 6% of their series.[9] Intracellular acid-fast bacilli in two choroidal granulomas were also seen at necropsy by Holland *et al.*[10] Choroidal mycobacterial disease in AIDS patients has also been described elsewhere.[11,12] The appearance of our patients, their use of aerosol pentamidine, and response or lack of progression with systemic antipneumocystis therapy leads us to believe that *P carinii* is more likely to be the primary infection in our six cases; however, coinfection with mycobacteria is possible. In the absence of reliable skin testing or antibiotic agents that could be used in a therapeutic trial, the diagnosis of *M avium* choroiditis can be made only on biopsy.[13] Since our patients generally had good vision, biopsy was not recommended. Because no cure for *M avium* infection exists, and there is no diagnostic test other than biopsy for its presence in the eye, the role of a thorough investigation for systemic atypical mycobacteria in such patients is unclear.

Patient 2 differed from our other patients. He had cryptococcal meningitis with bilateral optic neuropathy; choroidal lesions probably also represented cryptococcal infection. A similar case was described by Winward *et al.*[14] Cryptococcal choroiditis has been well documented in patients with and without AIDS.[14–19]

Other causes of choroidal lesions in AIDS patients must also be considered. Secondary syphilis can present as a multifocal choroiditis with large placoid foveolar lesions.[20–22] None of our patients had reactive rapid plasma reagin (RPR) of blood or CSF, but falsely negative serology can occur in AIDS patients.[23–25] Bilateral histoplasma chorioretinitis has been reported in an AIDS patient, but the clinical picture differed from that of our cases.[26]

Reticulum cell sarcoma can present with isolated multicentric choroidal lesions. Central nervous system lymphoma is common in AIDS patients, but choroidal involvement has not yet been reported.[27] Septic choroiditis can start as a multifocal choroiditis but would be expected to progress to uveitis and panophthalmitis.[28] Choroidal lesions can also be caused by metastatic carcinoma, sarcoidosis, Vogt-Koyanagi-Harada syndrome, or sympathetic ophthalmia.[29–31]

We have been impressed by two aspects of the choroiditis in our patients. Many lesions caused little or no visual problem even with the fovea directly involved and were reversible to some degree with therapy. Our only patient with severe visual loss had cryptococcal choroiditis with optic neuropathy.

Secondly, the finding of presumed *P carinii* choroiditis in an AIDS patient does not necessarily imply death within a few weeks as previously reported. None of our patients died precipitously; most survived several months after rapid systemic treatment for *P carinii*. Increased awareness of this marker for disseminated pneumocystis infection may allow for its earlier detection and treatment. Diagnostic imaging may reveal sites of disease amenable to biopsy, confirming dissemination of disease. Disseminated *P carinii* infection requires systemic treatment, probably on a long-term basis. Future investigation of ocular involvement in the beige mouse model of *M avium* infection may be helpful.[32]

1 Rao NA, Zimmerman PL, Boyer D, *et al* Study of *Pneumocystis carinii* choroiditis *Am J Ophthalmol* 1989, 107· 218–28

2 Macher AM, Bardenstein DS, Zimmerman L. *P carinii* choroiditis in a male homosexual with AIDS and disseminated pulmonary and extrapulmonary *P carinii* infection *N Engl J Med* 1987; 316: 1092.

3 Freeman WR, Gross JG, Labelle J, Oteken K, Katz B, Wiley CA. *Pneumocystis carinii* choroidopathy a new clinical entity *Arch Ophthalmol* 1989, 107: 863–7.

4 Raviglione MC, Garner GR, Mullen MP *Pneumocystis carinii* in bone marrow. *Ann Intern Med* 1988; 109. 253

5 Macher AM, Kovacs JA, Gill V, Roberts GD Bacteremia due to *Mycobacterium avium intracellulare* in the acquired immunodeficiency syndrome *Ann Intern Med* 1983; 99: 782–5.

6 Wong B, Edwards FF, Kiehn TE, *et al* Continuous high-grade *Mycobacterium avium-intracellulare* bacteremia in patients with the acquired immune deficiency syndrome *Am J Med* 1985; 78: 35–40

7 Wallace JM, Hannah JB. *M avium* complex infection in patients with AIDS *Chest* 1988; 93: 926–32

8 Agins B, Berman DS, Spicehandler D, EllSadr W, Simberkoff MS, Rahal JKJ. Effect of combined therapy with ansamycin, clofazimine, ethambutol, and isoniozid for *Mycobacterium avium* infection in patients with AIDS *J Infect Dis* 1989, 4: 784–7

9 Pepose JS, Holland GN, Nestor MS Acquired immune deficiency syndrome *Ophthalmology* 1985, 92: 472–84

10 Holland GN, Pepose JS, Pettit TH Acquired immune deficiency syndrome: ocular manifestations *Ophthalmology* 1983, 90: 859–73

11 Blodi BA, Johnson MW, McLeish WM, Gass JDM Presumed choroidal tuberculosis in an HIV infected host. *Am J Ophthalmol* 1989; 108: 605–7

12 Croxalto JO, Mestre C, Puente S, Gonzalez G Nonreactive tuberculosis in a patient with acquired immune deficiency syndrome *Am J Ophthalmol* 1986, 102: 659–60.

13 Abrams J, Schlaegel TF. The role of the isoniazid therapeutic test in tuberculous uveitis *Am J Ophthalmol* 1982, 94: 511–5.

14 Winward KE, Hamed LM, Glaser JS The spectrum of optic nerve disease in human immunodeficiency virus infection *Am J Ophthalmol* 1989, 107: 373–80

15 Kupfer C, McCrane E A possible cause of decreased vision in cryptococcal meningitis. *Invest Ophthalmol Vis Sci* 1974, 13. 801–4

16 Okun E, Butler WT. Ophthalmologic complications of cryptococcal meningitis *Arch Ophthalmol* 1961, 71: 96–101

17 Bisseru B, Bajaj A, Carruthers RH, Chhabra H Pulmonary and bilateral retinochoroidal cryptococcosis *Br J Ophthalmol* 1983, 67: 157–61.

18 Shields JA, Wright DM, Augsberger JJ, Wolkowicz MI Cryptoccocal chorioretinitis. *Am J Ophthalmol* 1980, 89: 210–8

19 Hiles DA, Font RL. Bilateral intraocular cryptococcosis with unilateral spontaneous regression *Am J Ophthalmol* 1968 65: 98–108

20 Halperin LS, Lewis H, Blumenkranz MS, Gass JDM, Olk R, Fine S. Choroidal neovascular membrane and other chorioretinal complications of acquired syphilis *Am J Ophthalmol* 1989; 108: 554–62

21 Schlaegel TF, Kao SF A review of 28 presumptive cases of syphilitic uveitis. *Am J Ophthalmol* 1982, 93: 412–4

22 Ross WH, Sutton HFS. Acquired syphilitic uveitis *Arch Ophthalmol* 1980, 98: 496–8

23 Klemer RC, Najarian L, Levenson J, Kaplan HJ. AIDS complicated by syphilis can mimick uveitis and Crohn's disease. *Arch Ophthalmol* 1987; 105: 1486–7.

24 Carter CB. Hamill RJ, Matoba AY. Syphilitic optic neuritis in a patient with a positive test for AIDS. *Arch Ophthalmol* 1987; 105: 1485–6.

25 Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus with Kaposi sarcoma. *Ann Intern Med* 1987; 107: 492–5

26 Macher A, Rodrigues M, Laplan W, *et al.* Disseminated bilateral chorioretinitis due to *Histoplasma capsulatum* in a patient with the acquired immunodeficiency syndrome *Ophthalmology* 1985; 92: 1159–64.

27 Gass JD, Sever RJ, Grizzard SW, *et al.* Multifocal pigment epithelial detachments by reticulum sarcoma. *Retina* 1984; 4: 135–43

28 Davis JL, Nussenblatt RB, Bachman DM. Endogenous bacterial retinitis in AIDS. *Am J Ophthalmol* 1989; 107: 613–23.

29 Marcus DF, Bovino JA, Burton TC. Sarcoid granuloma of the choroid *Ophthalmology* 1982, 89: 1326–30

30 Campo RV, Aaberg TM. Choroidal granuloma in sarcoidosis. *Am J Ophthalmol* 1984; 97: 419–27

31 Gass JDM, Olson CL Sarcoidosis with optic nerve and retinal involvement *Arch Ophthalmol* 1976; 94: 945–50

32 Gangadharam PR, Edwards CK, Murthy PS, Pratt PF. An acute infection model for *Mycobacterium intracellulare* disease using beige mice. *Am Rev Respir Dis* 1983; 127: 648–9.

Therapeutic outcome of patients suffering from malignant melanomas of the conjunctiva

P K Lommatzsch, R E Lommatzsch, I Kirsch, P Fuhrmann

Abstract

Eighty-one cases of conjunctival melanoma treated between 1960 and 1988 were studied to determine factors that might affect outcome in patients with such lesions. The therapeutic procedures performed were local excision (16), local excision followed by brachytherapy with Sr-90/Y-90 (32), local excision followed by cryotherapy with liquid nitrogen (16), brachytherapy with Sr-90/Y-90 (12), local excision followed by external beam irradiation (3), and local excision followed by brachytherapy and cryotherapy (2). The median follow-up period was 5·5 years (longest 26, shortest 1 year). Sixty two patients (76·5%) showed a complete regression of the melanoma, 19 (23·5%) developed recurrences, and 15 (18·5%) died from metastases. The melanomas had developed with almost equal frequency from a pre-existing naevus (25·9%), from primary acquired melanosis (25·9%), and 'de novo' (30·9%). Small tumours had a higher chance of regressing (80·6%) than larger ones (68·6%). The cumulative survival rate was 76% after five years and 60% after 10 years from any causes of death and 87·6% after five years and 76·3% after 10 years from deaths caused by metastases. Most deaths from metastases occurred within 5 years. At 88·5%, the cumulative survival rate of patients with small tumours (less than one quadrant of the bulbar conjunctiva and less than 2 mm thickness) was significantly higher than that of patients with larger tumours (more than one quadrant of the bulbar conjunctiva and/or more than 2 mm thickness) with 65% after eight years. Local excision followed by β ray irradiation (Sr-90/Y-90) or cryotherapy can be recommended as the treatment of choice. Nevertheless the behaviour of conjunctival melanomas remains unpredictable in individual cases.

Eye Hospital, Karl Marx University, Leipzig, German Democratic Republic
P K Lommatzsch
R E Lommatzsch
P Fuhrmann

Institute of Social Hygiene, Humboldt University Berlin (Charité), Otto-Grotewohl Strasse 1, 1040 Berlin, German Democratic Republic
I Kirsch

Correspondence to
P K Lommatzsch, Klinik fur Augenkrankheiten, Karl-Marx-Universitat Leipzig, Liebigstrasse 14, 7010 Leipzig, German Democratic Republic.

Accepted for publication
17 May 1990

Primary malignant melanomas of the conjunctiva are rare tumours, constituting only 2% of eye melanomas. This is why so 'much of what has been written about pigmented lesions of the conjunctiva is either anecdotal, speculative, or controversial'.[1] The controversial nature of this subject is reflected in different classifications of the lesion, in different modes of treatment, and in the uncertainty of many ophthalmologists in judging the clinical behaviour of any melanotic change of the conjunctiva.

The purpose of this study is to present clinical results obtained from 81 patients suffering from conjunctival melanoma in an attempt to provide a better understanding of the behaviour of these tumours and to raise unanswered questions on this topic.

Material and methods

Eighty one patients suffering from malignant melanoma of the conjunctiva were treated and followed up during 1960–88. All were examined by the authors. Included are patients of the University Eye Hospital (Charité) in Berlin (1960–76), from the Municipal Eye Hospital, Berlin-Buch (1976–81), and the University Eye Hospital, Leipzig (1981–8). In the early 1960s we decided to avoid any mechanical irritation of a suspected conjunctival melanoma. Thus for fear of provoking metastases five patients were treated with β irradiation without previous biopsy. Later we changed our mind and a biopsy was taken from all tumours before any radio- and cryotherapy.

The following therapeutic procedures were performed: local excision (16), local excision followed by brachytherapy with Sr-90/Y-90 (32), local excision followed by cryotherapy with liquid nitrogen (16), brachytherapy with Sr-90/Y-90 (12), local excision followed by radiotherapy with high energy electrons (3), and local excision followed by brachytherapy and cryotherapy (2). Altogether, exenteration was performed in six, enucleation in one, and lamellar keratoplasty in four patients.

We used β ray applicators of several shapes and sizes to cover the tumour completely.[2–5] The daily dose applied at the tumour surface was 10 Gy until a total dose of 150–200 Gy was delivered, depending on the thickness of the neoplasm. The radioactive source has to be brought into direct contact with the tumour after local anaesthesia. The irradiation time for the application of 10 Gy ranged from 40 s to 10 min. Cryotherapy was carried out at deep temperatures with liquid nitrogen. Contact freezing with applicators of several shapes (OKG 1) was performed in more extended tumours. A liquid nitrogen spray (OKG 3) was used to perform a triple freeze-thaw cycle. Each freezing time was 10 s to 1 min depending on the size of the tumour. Cryotherapy is recommended after surgical excision for treating possible residual invasive cells at the surgical margin.[6]

To describe the extent of the neoplasm the recommendations of the TNM classification were used only in part.[7] The histological specimens were examined by three pathologists (Professor G Goder of Berlin, Prosektor G Bauke of Berlin, and Dozent U Fuchs of Leipzig). Unfortunately some specimens of the 1960s were lost before reappraisal.

After treatment all the patients were followed up once a month. Later on, after stabilisation of the treated eye, we saw our patients at least once a year. In cases of death we questioned the family doctors or the local oncology service about the cause of death. The cumulative death rate was calculated by the life table method.[8 9]

Patients who died from metastases proved by necropsy, biopsy, or clinical examination were counted as tumour related deaths. All patients whose tumour shrank completely and in whom no recurrence was observed for at least one year were classified as locally cured cases. All cases without tumour regression or with new tumour formation and new tumour growth after local therapy were described as recurrences. In case of both local cure and of local recurrence metastases occurred.

Large tumours (more than one quadrant of the bulbar conjunctiva and/or more than 2 mm thick) were compared with small tumours (less than one quadrant of the bulbar conjunctiva and less than 2 mm thick) to verify the influence of tumour size on the cure rate, recurrence rate, and survival rate. The significance was examined by the χ^2 test and Mantel-Haenszel test.

Results

FREQUENCY AND INCIDENCE

The National Cancer Registry of the GDR (approximately 16·7 million) has 196 malignant melanomas of the conjunctiva on file (77 male and 119 female patients), registered between 1960 and 1985. No increase of frequency was noted during this time. Accordingly the incidence of malignant conjunctival melanomas can be assumed to be 0·08 per 100 000 population per year.

FOLLOW-UP PERIOD

The median follow-up period was 5·5 years (minimum one year, maximum 26 years). Forty four patients (54·3%) could be followed up for more than five years.

AGE AND SEX

The average age of all 81 patients was 55 years at the time of primary examination (minimum 21, maximum 93 years). The average age of the female patients was 60 years (minimum 31, maximum 93 years) and higher than that of the male patients with 51 years (minimum 21, maximum 78 years). There was a clear preponderance of 52 female patients (64·2%).

PRIMARY LOCALISATION, ORIGIN, AND TUMOUR SIZE

The primary tumour was located exclusively in the bulbar conjunctiva in 59 cases (73%). In addition the cornea was involved in four cases (5%), the tarsal conjunctiva in four (5%), the fornix in six (7%), and cornea and fornix in one case. In two patients (3%) the primary tumour was confined to the conjunctiva tarsi, and five patients (6%) had developed a primary malignant melanoma of the lacrimal caruncle.

The extent of the conjunctival melanomas before treatment was as follows:

Tumour involved maximum one quadrant of the bulbar conjunctiva	38 (46 9%)
Tumour involved more than one quadrant of the conjunctiva	16 (19 8%)
Tumour involved fornix, palpebral conjunctiva or caruncle	18 (22 2%)
Tumour extension into eyelid, cornea or orbit	8 (9·9%)
The extent of invasion could not be assessed	1 (1·2%)

Taking into consideration the patients' history and the clinical appearance of the lesions, we found the conjunctival melanomas had developed in 38 patients (46·9%) 'de novo', in 23 (28·4%) from a pre-existing naevus, and in 20 (24·7%) from primary acquired melanosis (PAM).

POSTSURGICAL HISTOPATHOLOGICAL EXAMINATION

The histopathological results of all tumours primarily excised and of all biopsies taken before radio- or cryotherapy were as follows:

Malignant melanoma confined to the conjunctiva and 2 mm or less in thickness	36 (44·5%)
Malignant melanoma confined to the conjunctiva but more than 2 mm in thickness	20 (24 7%)
Malignant melanoma of the conjunctiva with extension in eyelid, cornea, or orbit	15 (18·5%)
No malignant melanoma but primary acquired melanosis	1 (1·2%)
No histopathological examination was available	9 (11·1%)

Malignant transformation of a pre-existing naevus or primary acquired melanosis was suspected in 21 cases (25·9%) each, while 'de novo' development seemed most likely in 25 cases (30·9%). In 13 cases (16·1%) no information on the origin of the melanoma was available. These numbers differ only insignificantly from those based on clinical appearance.

THERAPEUTIC RESULTS

In 52 patients (64·2%) the tumour shrank completely after radiotherapy or did not recur after excision. Pigmentation was no longer traceable.

In another 10 eyes (12·3%) the tumour disappeared completely, but within the flat scar some pigmentation could be observed. In the remaining 19 cases (23·5%) the tumour either recurred after therapy or further growth could not be prevented.

1. Tumour regression. Altogether the conjunctival melanoma in 62 patients (76·5%) showed complete shrinkage or, after excision, no recurrence or remnants of the former tumour (Fig 1).

2. Recurrences. In 19 patients the conjunctival melanoma first receded but later recurred locally or tumour new growth remained uninfluenced. After repeated local therapy a complete regression of the recurrent tumour was finally obtained in nine cases. In 10 cases the tumour continued to grow, and in six patients exenteration was eventually necessary. Nine patients in this group died from metastases.

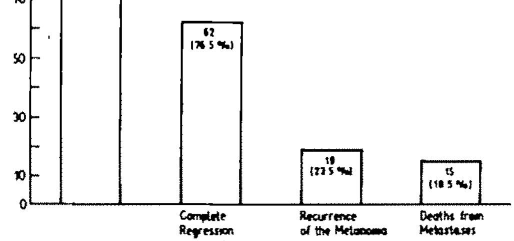


Figure 1 Therapeutic result of 81 patients with conjunctival melanoma (median follow-up 5·5 years).

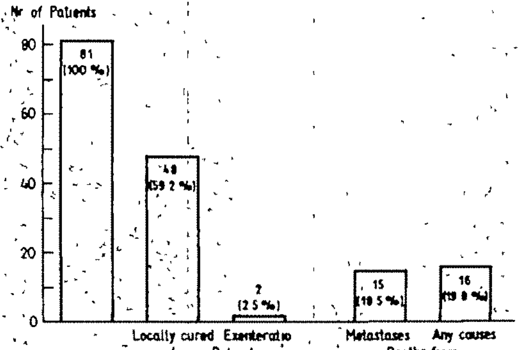


Figure 2 Living and dead patients of 81 cases with conjunctival melanoma (median follow-up 5·5 years).

3. *Deaths from metastases.* During 1960–88, 31 patients (38·3%) died, 15 of them (18·5%) from proved metastases (10 female, 5 male patients, Fig 2). In 10 cases metastases were diagnosed clinically; in five cases necropsy was performed. One patient died from hepatic carcinoma as a second malignant tumour. In 10 cases it was noted that the regional lymphnodes were involved before the patients died from general haematogenous metastases.

As shown in Figure 3 most of our patients died within five years of their first treatment. One patient died 11 years and another even 25 years later from proved metastases of the primary conjunctival melanoma. Deaths from metastases occurred at an average of 6·2 years (median 5 years) after the first treatment of the lesion. The patients' average age was 67 (minimum 33, maximum 82) years.

The preponderance of 11 advanced tumours of more than 2·0 mm thickness in those patients who died from metastases was significant ($\chi^2=4{\cdot}07$, $p<0{\cdot}05$).

SURVIVAL RATE

The survival rate was calculated by the life table method. It compared the cumulative survival rates of our patients with those of a population aged 55 on the average. An overall cumulative survival rate of 76% after 5 years and 60% after 10 years was obtained. As regards deaths caused by metastases only, the cumulative survival rates were 87·6% after 5 years and 76·3% after 10 years (Fig 4).

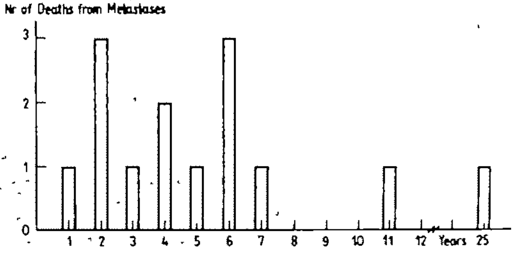


Figure 3 Metastatic deaths after beginning of treatment of 81 patients with conjunctival melanoma.

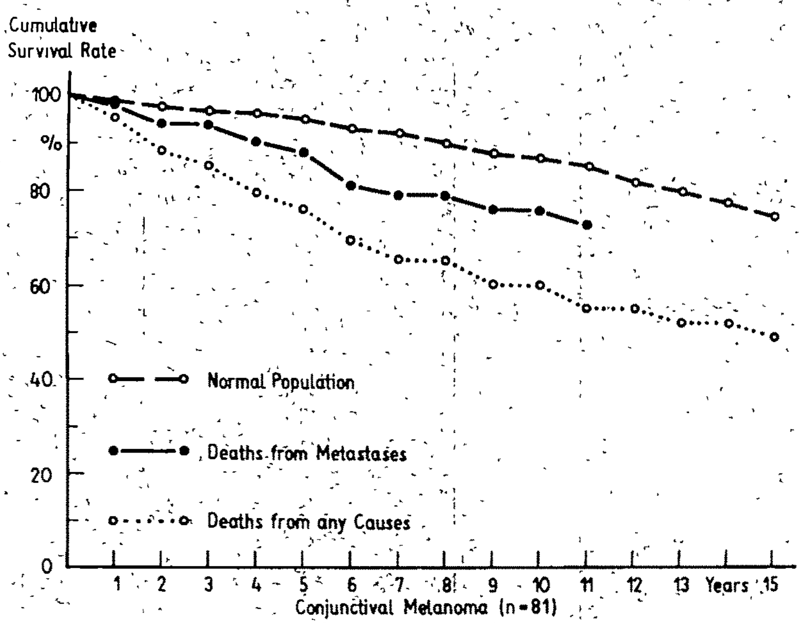


Figure 4 Cumulative survival rates of 81 patients with conjunctival melanoma in comparison with a population aged 55 years on the average.

TUMOUR EXTENT AND PROGNOSIS

Jakobiec[10] commented that tumour thickness is the 'sole sovereign prognosticator in conjunctival melanomas.' We therefore compared 36 small tumours (less than one quadrant of the bulbar conjunctiva and less than 2 mm thick) with 35 larger ones (more than one quadrant of the bulbar conjunctiva and/or more than 2 mm thick). This statistic includes only 71 cases with well defined postsurgical histopathological classification. As shown in Fig 5, the metastasis rate of the group with large tumours was 31·4%, almost three times higher than 11·1% of the group with small melanomas. This higher rate of larger tumours is statistically significant ($\chi^2=4{\cdot}40$; $p<0{\cdot}05$).

Figure 6 shows the result of a comparison between the cumulative survival rates of 38 patients with small tumours and those of 43 patients with an advanced lesion. After a follow-up period of eight years there was a statistically (Mantel-Haenszel test, $\chi^2=4{\cdot}15$; $p<0{\cdot}05$) higher survival of the group with smaller tumours (88·5%, SE 8·7%) than of that with advanced melanomas (65·0%, SE 10·6%).

TUMOUR ORIGIN AND PROGNOSIS

The metastasis rates according to the origin of the melanoma were as follows:

Melanoma derived from naevus	14·3% (3 patients)
Melanoma derived from PAM	33·3% (7 patients)
Melanoma derived 'de novo'	20·0% (5 patients)

The apparently higher incidence of melanomas derived from PAM in the patients with metastases is not statistically significant ($\chi^2=2{\cdot}32$; $p>0{\cdot}05$; df=2).

THERAPEUTIC SIDE EFFECTS

Local irradiation with β applicators (Figs 7A-E) and cryotherapy with liquid nitrogen have lethal effects not only on tumour cells but also on normal surrounding tissue. To keep side effects within reasonable limits excessive treatment should be avoided. The following side effects could be observed: Phthisis bulbi 1 (after cryotherapy); cataract 2; local lens opacity 7 (after β irradiation); symblepharon 2 (after cryotherapy);

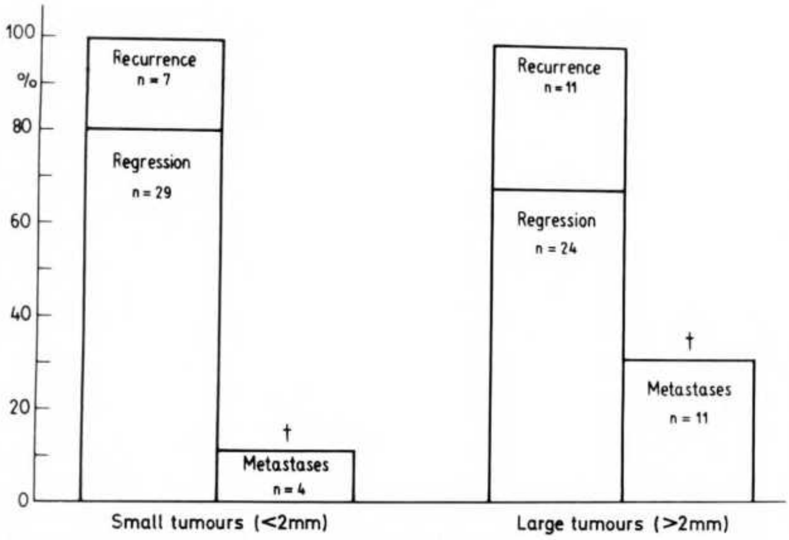


Figure 5 Regression, recurrence, and metastases after treatment of 36 small conjunctival melanomas in comparison with 35 larger ones.

corneal ulceration, descemetocele 2 (after cryotherapy); extented teleangiectasia of conjunctival vessels 3; iris atrophy 1 (after cryotherapy).

Discussion

It seems generally accepted that the development of malignant melanoma of the conjunctiva comprises three major groups. The lesions may derive from primary acquired melanosis, or from a pre-existing naevus, or develop 'de novo' where no antecedent lesion has been recognised. Therefore the pathologist needs a reliable clinical history for a comprehensive histological diagnosis, including the possible development of the tumour. This view may very well be an oversimplification, because Folberg *et al.*[11] found with the aid of further incisions of the lesions an associated naevus in approximately one-third of all melanomas developed from acquired melanosis. Some authors have related the prognosis of melanomas to their origin. Thus Yanoff and Fine[12] state that the mortality resulting from melanomas arising from naevi is 20%, whereas from melanomas arising from acquired melanosis or de novo it is 40%. Conjunctival melanomas have both spindle and epithelioid cell types. The latter do not have such an important influence on the degree of malignancy as in choroidal melanomas.

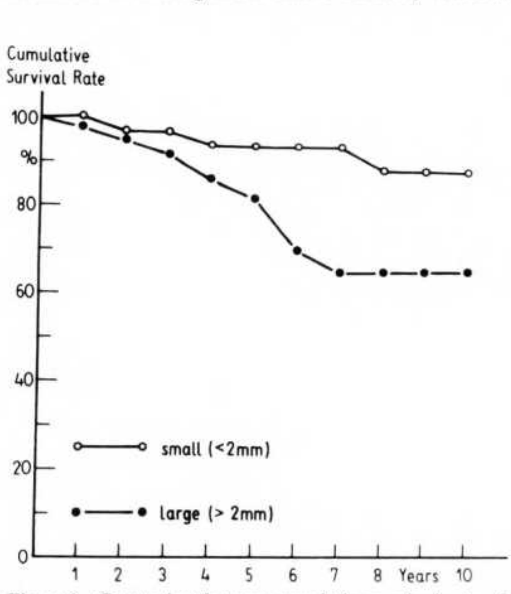


Figure 6 Comparison between cumulative survival rates of 38 patients with small and 43 with advanced conjunctival melanomas.

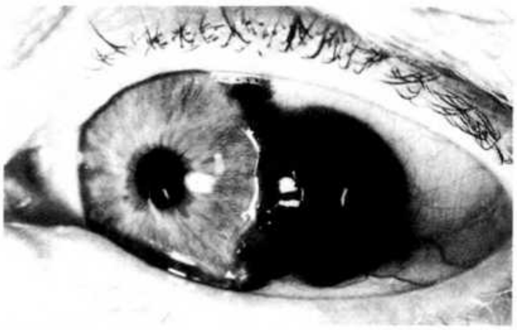


Figure 7A

Figure 7 (A) Conjunctival melanoma of an only eye, female patient aged 62 years. (B) Six months after brachytherapy with Sr-90/Y-90, 150 Gy. (C) Two years after treatment. (D) Eight years after treatment. (E) 11 years after treatment, visual acuity 1·0. No recurrence or metastases 15 years after irradiation.

The presence of a malignant melanocytic naevus is associated with a more favourable prognosis in patients with cutaneous melanomas. In contrast to this, Folberg *et al*[11] detected no such association between a better prognosis and the presence of a naevus in their series of conjunctival melanomas. In our cases the metastasis rates of melanomas developed from pre-existing naevi were 14·3%, de novo 20·0%, and from a primary acquired melanoma 33·3%. However, the highest metastasis rate of melanomas developing from PAM was statistically insignificant. We agree with Jakobiec,[10] Zimmerman,[13] and Folberg *et al*[11] not to apply the classification of cutaneous melanomas to the study of conjunctival melanomas. In particular the absence of stratification in the conjunctival substantia propria precludes the use of the microstaging system of Clark *et al*[14] in conjunctival melanomas.

Jakobiec[10] commented that tumour thickness is the most important prognosticator in conjunctival melanomas. Our results confirm this statement. The metastasis rate of conjunctival melanomas larger than 2 mm thick or involvement of fornix, palpebral conjunctiva, caruncle, or cornea was 31·4% and significantly higher than that of the group with smaller tumours, with 11·1%. Folberg *et al*[11] conclude from their careful evaluation of 131 patients with conjunctival melanoma that all lesions measuring at their

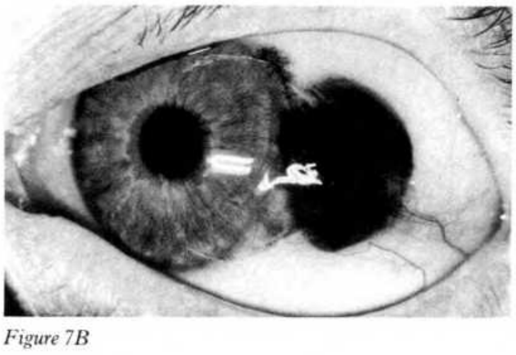


Figure 7B

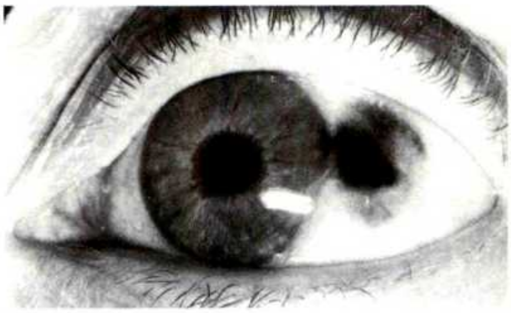


Figure 7C

greatest extent more than 0·8 mm are at high risk for the development of metastases – 29% and more. Though our findings are based on different material and methods, they are comparable with these results.

We can conclude that all lesions involving more than one quadrant of the bulbar conjunctiva and more than 2 mm thick are at high risk for development of metastases. On the other hand we observed lethal metastases in very small conjunctival melanomas and no metastases even after very thick tumours which had to be removed by exenteration. Thus it remains impossible for the ophthalmologist to obtain reliable prognostic signs to advise an individual patient. Both the evolution of primary acquired melanosis, which may wax and wane,[15] and the behaviour of conjunctival melanomas will often remain unpredictable.

The cumulative survival rate was 87·6% after 5 years and 76·3% after 10 years when only deaths caused by metastases are considered. These results come very close to the survival rates found by Folberg *et al.*[11] The overall mortality rate from metastases only in the 81 cases presented was 18·5%, and, from all causes of death, 38·3%. This is similar to the mortality rate of 26% published by Folberg *et al.*[11] This statistical analysis of the actuarial curves for two groups of our patients indicates that there is a significant difference between small and larger tumours during a follow-up of eight years. With 88·5% (SE 6·5%), small tumours give a better chance of survival than larger ones, with 65% (SE 10·6%) ($\chi^2=4\cdot15$; $p<0\cdot005$).

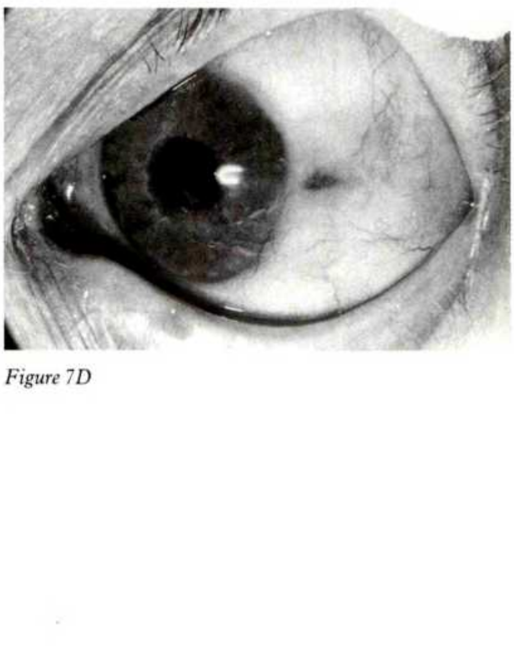


Figure 7D

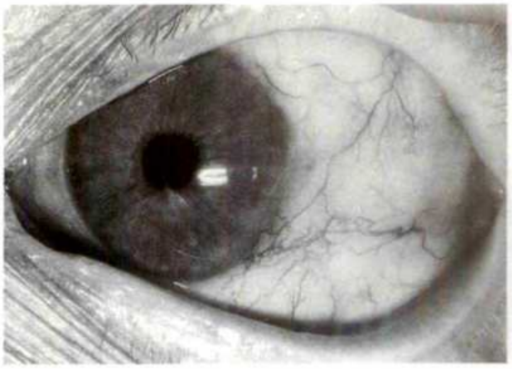


Figure 7E

Many recent attempts have been made in this subject to find reliable prognostic indicators to predict whether a particular conjunctival melanoma is likely to recur or to metastasize.[11 16 17] From the findings of the authors cited and the clinical observation presented in this paper it can be concluded that thickness and location of the neoplasm, its mitotic rate or the histopathological feature of an associated acquired melanosis must be regarded as prognostic signs. An international multicentric collaborative study would perhaps be suited to throw light on the unpredictable behaviour of this tumour.

1 Henkind D. Conjunctival melanocytic lesions: natural history. In: Jakobiec FA, ed. *Ocular and adnexal tumors.* Birmingham, Alabama: Aesculapius, 1978; 572–82.
2 Notter G. Das maligne epibulbäre Melanom. *Strahlentherapie* 1955; **96:** 518–537.
3 Lederman M. Radiotherapy of malignant melanomata of the eye. *Br J Radiol* 1961; **34:** 21–42.
4 Lommatzsch P. Beta irradiation of conjunctival melanomas. *Trans Ophthalmol Soc UK* 1977; **97:** 378–80.
5 Lommatzsch P. Beta-ray treatment of malignant epibulbar melanoma. *Graefes Arch Klin Exp Ophthalmol* 1978; **209:** 111–24.
6 Jakobiec FA, Brownstein S, Wilkinson RD. Katzin HM. Adjuvant cryotherapy for focal nodular melanoma of the conjunctiva. *Arch Ophthalmol* 1982; **100:** 115–8.
7 Harmer MH, Oosterhuis JA. *TNM classification of ophthalmic tumours.* Geneva: International Union Against Cancer, 1985.
8 Kiehl H, Kirsch I, Lommatzsch P. Das Überleben nach Behandlung des malignen Melanoms der Aderhaut: Vergleich von konservativer Therapie (106-Ru/106-Rh-Applikator) und Enukleation ohne und mit postoperativer Orbitabestrahlung, 1960–1979. *Klin Monatsbl Augenheilkd* 1984; **184:** 2–14.
9 Lommatzsch PK. β-irradiation of choroidal melanoma with 106-Ru/106-Rh-applicators. *Arch Ophthalmol* 1983; **101:** 713–7.
10 Jakobiec FA. Conjunctival melanoma: unfinished business. *Arch Ophthalmol* 1981; **98:** 1378–84.
11 Folberg R, McLean IW, Zimmerman LE. Malignant melanoma of the conjunctiva. *Hum Pathol* 1985; **16:** 136–43.
12 Yanoff M, Fine BS. *Ocular pathology. A text and atlas.* Philadelphia: Harper and Row, 1982: 800.
13 Zimmerman LE. The histogenesis of conjunctival melanomas. In: Jakobiec FA, ed. *Ocular and adnexal tumors.* Birmingham, Alabama: Aesculapius, 1978: 572–82.
14 Clark WH Jr, Folberg R, Ainsworth AM. Tumor progression in primary human cutaneous malignant melanomas. In: Clark WH Jr. Goldmann LI, Mastrangelo MJ, eds. *Human malignant melanoma.* New York: Grune and Stratton, 1979; 15–31.
15 Spencer WH, Zimmerman LE. Conjunctiva. In: Spencer WH, ed. *Ophthalmic pathology. An atlas and textbook.* Philadelphia, London, Toronto; Saunders, 1985: **1:** 192–220.
16 Fuchs U, Kivelä T, Liesto K, Tarkkanen A. Prognosis of conjunctival melanomas in relation to histopathological features. *Br J Cancer* 1989; **59:** 261–7.
17 Stefani FH. A prognostic index for patients with malignant melanoma of the conjunctiva. *Graefes Arch Clin Exp Ophthalmol* 1986; **224:** 580–2.

CALCUTTA CENTRAL LIBRARY

British Journal of Ophthalmology, 1990, 74, 620–623

MINI REVIEW

Endogenous posterior uveitis

The recent development of several animal models of endogenous uveitis has considerably advanced our understanding of the many clinical presentations of uveitis. For instance, it is now quite clear that, pathogenetically as well as clinically, anterior uveitis is a separate disorder from posterior uveitis. In contrast, despite the considerable heterogeneity of posterior uveitis syndromes, the evidence from experimental models suggests that each clinical entity may be a manifestation of one aspect of a common pathogenetic process which is represented by a limited set of uveoretinal responses to inflammatory stimuli.[1 2]

Many factors combine to produce uveitis. In anterior uveitis, a genetic predisposition is highlighted by the link with the major histocompatibility complex (MHC) class I antigen, HLA-B27,[3] while an association with infectious disease is suggested, particularly with regard to viral infection[4] and more recently Yersinia enterocolitis.[5] Most inflammatory diseases of the posterior segment are of unknown aetiology, though some such as retinal vasculitis may be linked with systemic disease such as sarcoidosis, or they may occur as part of a well described clinical disorder such as Behçet's disease.[6] Association with other diseases, however, does not equate with causation, and the lack of evidence implicating micro-organisms in most cases of endogenous posterior uveitis has led investigators to consider autoimmunity as a cause. Indeed, sympathetic ophthalmia, which represents one form of endogenous posterior uveitis, was probably the first autoimmune disease described.[7]

Even in this regard, however, the distinction between autoimmune disorders (or disturbances of immune regulation) and infectious disease is becoming blurred. Current hypotheses concerning the aetiology of autoimmune diseases include several variations on the theme of altered immune regulatory mechanisms induced by invading micro-organisms. Sequence homology between epitopes on foreign and self-antigens for instance, may be sufficient to initiate an autoimmune disease via cross-reacting anti-idiotypic T or B cells which persist long after the inciting micro-organisms have been eliminated. Molecular mimicry of this type has recently been demonstrated in experimental autoimmune uveitis induced by retinal antigen-related peptides bearing sequences which resemble peptides from certain viruses.[8] All immune responses, including those against autoantigens, require the appropriate MHC haplotype for their induction, and this explains the genetic predisposition to (autoimmune) disease. Perhaps the strongest MHC association with disease in man yet described is that between HLA-A29 and birdshot retinochoroidopathy (>90%),[9] a discrete clinical entity included within the term endogenous posterior uveoretinitis.[10]

It is clear therefore that, although immune mechanisms are currently under intensive investigation in uveoretinal inflammatory disease, they do not necessarily exclude an infectious aetiology, and they must be viewed within the context of genetic and environmental factors. In the final analysis it may not be possible, or even necessary, to unravel all the possible threads in the pathogenesis of uveitis (or indeed of any 'autoimmune' disease). Rather it may be more appropriate to define more clearly the cellular mechanisms involved in the production of tissue damage, so that these processes can be interrupted by more specific and/or selective immunotherapy.

In this brief review similarities are drawn between various clinical forms of endogenous posterior uveitis and experimental models of autoimmune uveoretinitis (EAU). Certain aspects of the immunopathology are discussed with particular reference to the mechanisms of tissue damage. In addition the role of clinical immunological testing in posterior uveitis is appraised, while possible future directions for immunointervention are indicated.

Clinical presentation of endogenous posterior uveitis

Endogenous posterior uveitis includes several discrete clinical entities (Table 1) which at first sight might seem to be unrelated. Pars planitis (intermediate uveitis), for instance, involves predominantly the peripheral retina and vitreous base, and characteristically is associated with vitreous inflammatory cell infiltrates (snowballs) and extensive subretinal chorioretinal infiltrates. Careful examination and fluorescein angiography will, however, show that many of these cases also have signs of peripheral retinal vasculitis, while visual loss is most frequently due to macular oedema, itself usually a manifestation of increased perifoveal capillary leakiness.

Sympathetic ophthalmia is characterised by the focal chorioretinal nodule or microgranuloma – the Dalen-Fuchs nodule. These typically accumulate as healed scars within the fundus after a short self-limiting period of active inflammation. Similar nodules are observed in sarcoid uveoretinitis,[11] in Vogt-Koyanagi-Harada's disease during the phase of resolution,[12] and in the less well defined disorder of diffuse choroiditis. They are also frequently the cause of exacerbations of vitritis in cases of 'intermediate' uveitis or pars planitis, where one or two small, round, white foci in the equatorial or pre-equatorial fundus may be sufficient to cause symptoms of floaters. They often escape detection, however, because they are short-lived and self-limiting, and may disappear leaving virtually no trace. When they occur in large numbers, as in sympathetic ophthalmia, less so in sarcoidosis, they have a characteristic appearance of fluorescein angiography during the active phase; hypofluorescent choroidal 'spots' in the early sequence with late hyperfluorescence.[13] Healed, inactive lesions are overlaid by depigmentated retinal pigment epithelium and appear as pigment epithelial defects on fluorescein angiography.

Retinal vasculitis involving the posterior pole may present as an 'idiopathic' disorder or as part of a disease entity such as sarcoidosis, Behçet's disease, multiple sclerosis, systemic lupus erythematosus. The vasculitis may affect small or large

Table 1 Endogenous posterior uveitis – clinical syndromes

Intermediate uveitis
Pars planitis
Idiopathic retinal vasculitis
Sarcoid retinitis/vasculitis
Birdshot choriodoretinopathy
Beçhet's disease
Vogt-Koyanagi-Harada disease
Some pigment epitheliopathies
Acute retinal necrosis

Diffuse uveitis
Panuveitis
Choroiditis
  Discrete
  Serpiginous

vessels and occurs usually as a phlebitis with retinal haemorrhages. Less frequently, an arteritis and phlebitis occur, with widespread retinal infiltrates and ischaemia even to the point of retinal necrosis. Retinal vasculitis rarely occurs in isolation. Careful examination will reveal that chorioretinal infiltrates similar to those in sympathetic ophthalmia are present. In addition, vitreous inflammatory cells are almost a prerequisite for the differentiation of retinal vasculitis from other retinal vascular thrombotic disorders.

Some forms of endogenous posterior uveitis appear to be predominantly choroidal, such as birdshot choroidoretinopathy, in which the hallmark is the widespread distribution of subretinal focal infiltrates and patches of retinal pigment epithelial atrophy. Others appear to be predominantly retinal, such as retinal vasculitis and acute retinal necrosis; while others still produce mainly vitreous cellular infiltration with minimal involvement of the ocular coats.

Some disorders appear to have a clear infectious aetiology such as herpes simplex-induced acute retinal necrosis, cytomegalovirus retinitis, and toxoplasmosis retinochorioditis, though the evidence for the last has become less compelling in the light of recent data showing no clear serological differences between clinically 'toxoplasma' infected patients and healthy controls.[14] Most uveitis syndromes, however, are of unknown aetiology and much of the reported histopathology has been concerned with endstage disease.[15] Immunohistopathological studies have shown that T cells, particularly T helper (CD4+) cells, and monocytes predominate in many lesions such as the Dalen-Fuchs nodule in sarcoidosis and in sympathetic ophthalmia.[16] Studies of active retinal vasculitis or pars planitis have not been reported in detail but some interesting studies of choroidal changes have been reported in Vogt-Koyanagi-Harada disease.[17] In general, however, the available histological data have supported the concept of an immunologically mediated process in most forms of posterior uveitis.

In addition, despite the differences in clinical presentation, most forms of posterior uveitis have four cardinal features: (1) vitreous inflammatory cells and exudate (vitreous haze); (2) focal choroidoretinal infiltrates; (3) retinal vasculitis; and (4) macular oedema. In some forms there may be a greater emphasis on one or more of these features such as retinal vasculitis or, in birdshot choroidoretinopathy, focal chorioretinal infiltrates. In other forms additional features may be present, such as retinal necrosis, exudative retinal detachment (in Vogt-Koyanagi-Harada disease), or subretinal and preretinal neovascularisation. As will be seen from the discussion below, however, these manifestations represent the spectrum of choroidoretinal responses to an inflammatory stimulus, and this limited clinical set of responses is essentially the same whether the stimulus is immunological, chronic infectious, or a combination of both.

Experimental models of posterior uveoretinitis

Since the pioneering work of Wacker and his colleagues[18] demonstrated unequivocally that proteins within the retina could induce an autoimmune uveoretinitis, several antigens have been described including retinal S (soluble) antigen, interphotoreceptor retinol binding protein (IRBP), opsin, and rhodopsin (for review see Gery *et al*).[19] Complete amino acid sequence data for these proteins are now available,[20–22] and considerable information on the immunodominant epitopes of two of them (S-antigen and IRBP)[23–25] is known. A single injection of any one of these antigens, when emulsified with Freund's adjuvant and injected into the subcutaneous tissues of an experimental animal, will induce an organ-specific autoimmune inflammation (which includes the pineal gland, the invertebrate third eye). The degree of inflammation varies with the nature of the antigen, the species, and strain (ie, MHC type) of animal, the dose of antigen, the degree of immunosuppression, and the conditions for immunisation[1 2] (Table 2). In addition, both acute and chronic uveoretinitis models have been developed.[26–28]

Table 2 Predominant form of experimental autoimmune uveoretinitis in each animal with different autoantigen

	Antigen		
Model	*S*	*IRBP*	*Opsin*
Rat	Acute	Acute	Moderate
Mouse	Chronic	Chronic	ND
Guinea-pig	Variable	Weak	Weak
Rabbit	Mild	Mild	ND
Monkey	(Retinal) chronic	(Choroidal) chronic	Moderate

IRPB=interphotoreceptor retinal binding protein ND=not done

Despite the lack of homology between the different antigens, the clinicopathological features of the uveoretinal inflammatory disease in EAU are remarkably similar. An important corollary to this is that each antigen can induce the full range of clinical and pathological features seen in human posterior endogenous uveitis.[2] For instance, the earliest lesion in both S-antigen and IRBP-induced EAU is a single cell infiltrate in the photoreceptor layer, the site of the target antigen(s).[27] A characteristic lesion following this infiltration of cells is the focal chorioretinal nodule, similar to the human Dalen-Fuchs nodule. These develop and subside over a short time span (2-3 weeks), may occur in several places at the same time and sequentially, and progressively increase in number until the outer retina is extensively damaged and replaced by patches of fibrovascular scar tissue. In animals with a retinal vasculature, such as the rat and monkey,[26 29] vasculitis is frequently observed as an early manifestation. Retinal vasculitis may involve a few small vessels or extend to many vessels and the degree of involvement depends on the dose of antigen. The clinical and fluorescein angiographic features of experimental retinal vasculitis are identical to human retinal vasculitis.

Acute inflammation with massive exudative retinal detachment may be observed with high doses of antigen in susceptible animals and is reminiscent of Vogt-Koyanagi-Harada disease in the acute phase. Acute necrosis of the retina may also occur.[2] Acute EAU in Lewis rats has been the most extensively investigated model so far, but it represents only one type of uveoretinitis and is probably not the most characteristic of human endogenous uveitis.

In contrast, recent studies have demonstrated that chronic EAU can be induced in certain strains of mouse,[28] in guinea-pigs,[27] and in rats with antigens prepared in the presence of protease inhibitors.[2] In these models subretinal neovascularisation may occur in the late stages[2 28] in precisely the same manner as occurs in human birdshot retinochoroidopathy.

A paradigm for human posterior uveitis has therefore emerged in that a single antigen can elicit the same range of clinical pathological manifestations in the experimental animal as are seen in human disease, and that several different antigens can induce the same limited set of responses. The factors which determine the clinical presentation, therefore, probably relate less to the nature of the antigen than to the dose of antigen, the susceptibility of the host, the genetic predisposition and the prevailing environmental conditions. Furthermore, it is likely that, although the initiating agent may differ, the mechanism of disease production is probably similar in most of these disorders but is modified by one or more of these factors. A relationship to 'infectious' forms of uveoretinitis may be envisaged whereby the inital microorganism-associated retinal inflammation induces breakdown of the blood-retinal barrier and permits access of polyclonally activated autoreactive T cells to previously sequestered and potent retinal autoantigens, thereby setting up an autoimmune uveoretinitis which becomes self-perpetuating.[30]

Relevance of experimental uveitis to clinical disease

The initial enthusiasm for detecting autoantibodies to retinal antigens[31,32] and for demonstrating cell mediated immunity to retinal antigens[33] has become tempered by the observation that antiretinal antibodies occur normally in the general population[34,35] and also that circulating autoreactive T cells to S-antigen and to IRBP are to be found in healthy individuals.[35,36] Indeed, it has been suggested that high levels of antiretinal antibodies may be protective against the more severe forms of endogenous uveitis[34,37] and that, in cases of active sympathetic ophthalmia and Behçet's disease, antiretinal antibodies may in fact be decreased (Forrester, Noble, Chamberlain, *et al*, unpublished observations). These results are not surprising, since only a very small proportion of serum immunoglobulins and circulating T cells are actually autoreactive, and an even smaller proportion will be specific for retinal antigens. Therefore, even if these antibodies and/or cells were proportionally increased, for example, by a factor of 10, they would probably remain below the detectable limit due to the wide range of values which occur in the normal population.

Similarly, other immunological tests of a less specific nature have been unrewarding in studies of endogenous uveitis. These include enumeration of total T and B and T cell subsets, and T/B cell proliferation studies to non-specific antigens.[38] For the reasons detailed above it is unlikely that such studies would be informative.

More recently markers of T cell activation have become available, such as the MHC class II surface antigen and the interleukin-2 (IL-2) receptor. These markers have been shown to occur more frequently on circulating T cells in patients with endogenous uveitis,[39] and these data would coincide with current concepts of a generalised increase in lymphocytic activation in inflammatory disease. According to this notion 'activated lymphocytes, including activated autoreactive lymphocytes, could gain access to a tissue through defects in the blood-tissue barrier or more probably, through changes in the surface adhesiveness of the local vascular endothelium.[30,40] If invasive autoreactive lymphocytes come in contact with their respective autoantigen, local clonal T cell expansion would occur with considerable lymphokine production and active recruitment of further T cells and cytotoxic mononuclear cells. A focus of tissue damage with proliferating cells that it, a microgranuloma) would ensue. Since this process, at least initially, occurs at a local microscopic tissue level, it is not surprising that these changes fail to be reflected in the levels of circulating lymphocytes and autoantibodies. The only clue to such a mechanism might be that the overall level of 'activated' lymphocytes in the circulation would in some cases be increased.

Therefore, although endogenous uveitis has been resistant to the label of an 'autoimmune' disease by conventional criteria of autoantibodies and defects in T and/or B cells, there can be little doubt that immunological mechanisms play a major, if not a primary, role in the disease. Firstly, immunohistological studies show considerable involvement of various T cell subsets in many forms of the disease. Secondly, the clinical and pathological features of all types of human uveitis show extensive similarity to the various forms of experimental autoimmune uveoretinitis, induced by recognised retinal autoantigens. And, thirdly, many forms of endogenous uveoretinitis (and experimental autoimmune uveoretinitis) respond preferentially to immunosuppressive therapy, whether it is relatively broad spectrum as with systemic steroids and azathioprine, or more selective as with the CD4+ T cell inhibitor, cyclosporin A. These observations should direct us in our search for more effective therapy.

Possible immunotherapeutic approaches

The possibilites for intervention in immunologically mediated diseases are several. The aim in immunotherapy is to be as selective as possible in inhibiting the tissue damaging components of the autoimmune response, while sparing the normally functioning cellular immune responses which are required for defence against foreign antigens. Immunomodulation may be achieved by drugs or may be more specifically directed against the autoantigen if this is known. For instance, in experimental allergic encephalomyelitis, which is an autoimmune disease induced by myelin basic protein and has certain similarities to multiple sclerosis, inhibition of the disease can be induced by 'designer' peptides which block the binding site for autoantigens on the MHC molecule of the antigen presenting cell.[41,42] An alternative approach is to use monoclonal antibodies directed against surface molecules involved in T cell receptor recognition (particularly if they can be 'humanised' by structural manipulation)[43,44] or against the antigen itself as with EAU.[45,46] Intervention in this case may be mediated either by direct interaction with the antigen[45] or via an anti-idiotypic mechanism.[46] Therapy aimed at inhibiting interaction between the 'activated' lymphocyte and the endothelium – that is, at the site of blood-tissue barrier – is also possible, as has been shown recently in the case of antibodies to intercellular adhesion molecule-1 (ICAM-1) to reduce the severity of the immune response in a primate model of asthma.[47]

At present these potential therapeutic strategies remain essentially experimental in relation to human uveitis. Of more immediate interest, however, are recent advances in drug based immunointervention in which increasingly selective immunosuppression is employed. In this regard, the T cell inhibitor for cyclosporin A (CsA) has been used successfully to control endogenous uveitis both experimentally[48] and clinically in cases which had become steroid resistant or intolerant.[49-51] Two major problems arise in relation to CsA therapy for uveitis, namely, nephrotoxicity, and rebound uveitis after sudden withdrawal of the drug. Nephrotoxicity is reduced but is still significant if low dose (<5 mg/kg body weight) CsA therapy is employed. Furthermore, patients at risk of developing nephrotoxicity may be identified by the clear link with hypertension which has recently been shown.[51] That is, if the patient remains normotensive during therapy with CsA, then it is likely that he will escape renal dysfunction.

Some of the newer immunosuppressants may be less nephrotoxic, such as FK506, an inhibitor of T helper cells with an activity similar to CsA but at lower doses. In liver and renal transplant patients, FK506 has been shown to be remarkably free of nephrotoxicity,[52] but studies in autoimmune disease have not yet been initiated. Other macrolide immunosuppressants such as rapamycin may also have potential in the therapy of autoimmune uveitis.

It can be seen therefore that, although we do not know precisely the nature of the antigens, either foreign or self antigens, involved in the pathogenesis of posterior uveitis, we now have a greater understanding of the mechanisms of immunologically mediated uveoretinal inflammation which has been gained from the study of models of EAU and has led to a more rational and direct therapeutic approach.

J V FORRESTER

Department of Ophthalmology,
University of Aberdeen,
Medical School,
Foresterhill,
Aberdeen AB9 2ZD

1 Forrester JV Chronic intraocular inflammation. *Trans Ophthalmol Soc* 1985; **104:** 250–5
2 Forrester JV, Liversidge J, Dua HS, Towler H, McMenamin PG Comparison of clinical and experimental uveitis *Curr Eye Res* 1990; **9** (suppl): 75–84
3 Feltkamp TEW HLA antigens and uveitis *Eye* in press
4 Byrom MA, Campbell MA, Hobbs JR, *et al.* T and B lymphocytes in patients with acute anterior uveitis and ankylosing spondylitis, and in their household contacts. *Lancet* 1979; **ii:** 601–3
5 Wakefield D, Stahlberg TH, Toivanen A, Granfors K, Tennant C Serologic evidence of yersinia infections in patients with anterior uveitis. *Arch Ophthalmol* 1990; **108:** 219–21.
6 BenEzra D, Nussenblatt RB. Ocular manifestations of Behçet's disease. *J Oral Pathol* 1978; **7:** 431–42
7 Faure JP Autoimmunity and the retina. *Curr Eye Res* 1980; **2:** 215–301.
8 Singh VK, Kalra HK, Yamaki K, Abe T, Donoso LA, Shinohara T Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. *J Immunol* 1990, **144:** 1282–7.
9 Priem HA, Kijlstra A, Moeus L, Baarsma GS, de Lacy JJ, Oosterhuis JA HLA typing in birdshot chorioretinopathy *Am J Ophthalmol* 1988; **105:** 182–5
10 Priem HA, Oosterhuis JA. Birdshot chorioretinopathy. clinical characteristics and evolution. *Br J Ophthalmol* 1988; **72:** 646–59
11 Chan C-C, Metzig R, Palestine A, Kuwabara T, Nussenblatt RB Immunohistopathology of ocular sarcoidosis *Arch Ophthalmol* 1987; **105:** 1398–402.
12 Inomata H, Sakamoto T. Immunopathological studies of Vogt-Koyanagi-Harada disease with sunset sky fundus *Curr Eye Res* in press.
13 Sharp DC, Bell RA, Patterson E, Pikerton RMH Sympathetic ophthalmia. histopathologic and fluorescein angiographic correlation *Arch Ophthalmol* 1984, **102:** 232–5
14 Kijlstra A Immunological testing in uveitis. *Eye* in press
15 Lightman S, Chan C-C. (1989) Immunopathology of ocular inflammatory disorders In. Lightman, S, ed *Immunology of eye diseases*. London, Kluwer, Academic, 87–9
16 Jakobiec F, Marboe C, Knowles D, Iwamoto T, Harrison W, Chang S, Coleman D Human sympathetic ophthalmia *Ophthalmology* 1983, **90:** 76–95
17 Inomata H Necrotic changes of choroidal melanocytes in sympathetic opthalmia *Arch Ophthalmol 1988*, 106: 239–42.
18 Wacker WB, Donoso LA, Kalsow CM, Yankeeloo JA, Organisciack DT. Experimental allergic uveitis. Isolation, characterisation and localisation of a soluble uveitopathogenic antigen from bovine retina. *J Immunol* 1977; **119:** 1949–58
19 Gery I, Mochizuki M, Nussenblatt R. Retinal specific antigens and the immunopathologic process they provoke. *Prog Retinal Res* 1986; **5:** 75–109.
20 Shinohara T, Dietzschold B, Craft CM, *et al* Primary and secondary structure of bovine retinal S antigen (48K protein). *Proc Natl Acad Sci USA* 1988; **84:** 6975–9.
21 Borst DF, Redmond TM, Elser JE, *et al.* Interphotoreceptor retinoid-binding protein (IRBP). glue characterisations; protein repeat structures and its evolution *J Biol Chem* 1989; **264:** 1115–9.
22 Kuhn H Interactions between photoexcited rhodopsin and light-activated enzymes in rods *Prog Retinal Res* 1984; **3:** 123–56
23 Donoso LA, Merryman CF, Sery TW, *et al.* S-antigen: characterisation of a pathogenic epitope which mediates experimental autoimmune uveitis and pinealitis in Lewis rats. *Curr Eye Res* 1987; **6:** 1151–9
24 Gregerson DS, Obritsch WF, Fling SP. Identification of a uveitogenic cyanogen bromide peptide of bovine retinal S-antigen and preparation of a uveitogenic, peptide specific T cell line. *Eur J Immunol* 1987; **17:** 405–11
25 Sanui H, Redmond TM, Kotake S, *et al* Identification of an immunodominant and highly immunopathogenic determinant in the retinal interphotoreceptor retinoid-binding protein (IRBP). *J Exp Med* 1989, **169:** 1947–60
26 De Zozak Y, Sakai J, Thillaye B, Faure JP. S-antigen-induced experimental autoimmune uveoretinitis in rats *Curr Eye Res* 1981; **1:** 327–40.
27 Forrester JV, Borthwick GM, McMenamin PG. Ultrastructural pathology of S-antigen uveoretinitis *Invest Ophthalmol Vis Sci* 1985, **26:** 1281–92.
28 Caspi RR, Roberge FH, Chan CC, *et al* A new model of autoimmune disease *J Immunol* 1988; **140:** 1490–5.
29 Nussenblatt RB, Kuwabara T, de Monasterio FM, Wacker WB S-antigen uveitis in primates. A new model for human disease *Arch Ophthalmol* 1981, **99:** 1090–2
30 Liversidge J, Sewell HF, Forrester JV Interactions between lymphocytes and cells of the blood-retina barrier: mechanisms of T lymphocyte adhesion to human retinal capillary endothelial cells and retinal pigment epithelial cells in vitro. In press
31 Gregerson DS, Abrahams IW, Thirkill CE Serum antibody levels of uveitis patients to bovine retinal antigens *Invest Ophthalmol Vis Sci* 1981, **21:** 669–80
32 Uusitalo RJ, Stjernschantz J, Mahlberg K, *et al* Serum antibody level to S-antigen in children with chronic uveitis *Br J Ophthalmol* 1985; **69:** 212–6
33 Nussenblatt RB, Gery I, Ballintine EJ, Wacker WB Cellular immune responsiveness of uveitis patients to retinal S-antigen *Am J Ophthalmol* 1980; **89:** 173–9.
34 Forrester JV, Stott D, Hercus K. Naturally occuring antibodies to bovine and human retinal S-antigen a comparison between uveitis patients and healthy volunteers *Br J Ophthalmol* 1989, **73:** 155–9
35 Doekes G, van der Gaag R, Rothova A van Kooyk Y, *et al* Humoral and cellular immune responsiveness to human S antigen in uveitis *Curr Eye Res* 1987, **6:** 909–19
36 Hirose S, Tanaka T, Nussenblatt RB, *et al* Lymphocyte responses to retinal-specific antigens in uveitis patients and healthy subjects *Curr Eye Res* 1988, **7:** 393–403
37 Dumonde DC, Kasp-Grochowska E, Graham E, *et al* Anti-retinal autoimmunity and circulating immune complexes in patients with retinal vasculitis *Lancet* 1982; **ii:** 787–92
38 Froebel KS, Armstrong SS, Urbaniak SJ, Forrester JV An investigation of the general immune status and specific immune responsiveness to retinal S-antigen in patients with chronic posterior uveitis *Eye* 1989, **3** 263–70
39 Deschennes J, Char DH, Kalita S. Activated T lymphocytes in uveitis *Br J Ophthalmol* 1988, **72:** 83–7
40 Pab ST, Horst E, Scheper RJ, Meijer GJLM Mechanisms of lymphocyte migration and their role in the pathogenesis of disease *Immunol Rev* 1989; **108:** 112–33
41 Urban JL, Horvath SJ, Hood L Autoimmune T cells immune recognition of normal and variant peptide epitopes and peptide-based therapy *Cell* 1989, **59:** 257–71
42 Wraith DC, Smilek DE, Mitchell DJ, Steinman L, McDevitt HO Antigen recognition in autoimmune encephalomyelitis and the potential for peptide-mediated immunotherapy *Cell* 1989; **59** 247–55
43 Depper JM, Leonard WJ, Waldmann TA, Greene WC Blockade of the interleukin-2 receptor by anti-Tac antibody. inhibition of human lymphocyte activation. *J Immunol* 1983; **131:** 690–6
44 Reichmann L, Clark M, Waldmann H, Winter G Reshaping human antibodies for therapy. *Nature* 1988; **332:** 323–7.
45 Dua HS, Sewell HF, Forrester JV The effect of retinal S-antigen-specific monoclonal antibody therapy on experimental autoimmune uveoretinitis (EAU) and experimental autoimmune pinealitis (EAP) *Clin Exp Immunol* 1989; **75:** 100–5
46 De Kozak Y, Mirshahi M, Boucheix C, Faure JP, Letts LG, Rothlein R Prevention of experimental autoimmune uveoretinitis by active immunisation with autoantigen-specific monoclonal antibodies. *Eur J Immunol* 1987, **17:** 541–7
47 Wegner CD, Gundel RH, Reilly P, Haynes N Intercellular adhesion molecule-1) (ICAM–1) in the pathogenesis of asthma *Science* 1990; **247:** 456–9
48 Nussenblatt RB, Rodrigues MM, Walker WB, *et al* Cyclosporin A inhibition of experimental autoimmune uveitis in Lewis rats *J Clin Invest* 1987, **67:** 1228–31.
49 Nussenblatt RB, Palestine AG, Chan CC Cyclosporin A therapy in the treatment of intraocular inflammatory disease resistant to system corticosteroids and cytotoxic agents *Am J Ophthalmol* 1983, **96:** 275–82
50 Towler HM, Cliffe AM, Whiting PH, Forrester JV Low dose cyclosporin A therapy in chronic posterior uveitis. *Eye* 1989, **3:** 282–7
51 Towler HM, Whiting PH, Forrester JV. Combination low dose cyclosporin A and steroid therapy in chronic intraocular inflammation *Eye* in press
52 Thomson AW FK506 enters the clinic *Immunol Today* 1990; **11:** 35–6

British Journal of Ophthalmology, 1990, **74**, 624–628

CASE REPORTS

Malignant fibrous histiocytoma of the conjunctiva*

Jacob Pe'er, Shmuel Levinger, Michael Ilsar, Harold Climenhaga, Elimelech Okon

Abstract

Malignant fibrous histiocytoma (MFH) of the conjunctiva is an extremely rare tumour, and only three previous cases have been reported. We describe two patients with MFH of the conjunctiva: a 58-year-old white male with epibulbar tumour who had exenteration and is alive after five years' follow-up, and a 3½-year-old African girl with xeroderma pigmentosum and an MFH of her right eye conjunctiva, the first reported case of this association. The characteristics and the methods of diagnosis of MFH are discussed.

Fibrous histiocytoma (FH) of the conjunctiva is a rare benign tumour, and only 10 such previous cases have been described.[1-8] Two cases of conjunctival FH[9 10] showed a benign histological appearance but a malignant clinical course. Malignant fibrous histiocytoma (MFH) of the conjunctiva is extremely rare, and only three cases have been reported.[11-13] Five cases of FH were located in the eyelids.[14-17] Orbital cases of FH are considered to be the commonest primary mesenchymal orbital tumour of adults.[18]. We report here two cases of malignant fibrous histiocytoma of the conjunctiva.

Case reports

CASE 1

Clinical history. A 58-year-old man presented in February 1984 with a mass in the right eye of several months' duration. One year earlier he had been examined by another ophthalmologist, complaining of periocular itching. He was noted at that time to have scarring of the conjunctiva secondary to trachoma, and a small 'raised whitish limbal area' at 2 o'clock, but there was no mention of an epibulbar mass or a pterygium. Three months later a physician elsewhere removed a 'pterygium'. No histopathology report was available. On examination in February 1984 his corrected visual acuity was counting fingers (CF) at 2 m RE and 6/9 LE. A large epibulbar mass (approximately 15×10×4 mm) was present at the superonasal limbus, overlapping the semiopaque cornea by 2 mm. This mass transilluminated but did not appear cystic. There was no proptosis or displacement of the eye. The lid and corneal scarring were unchanged. Ocular motility was normal.

The mass was removed in piecemeal fashion. It was greyish and was not encapsulated. Following the initial pathology report of MFH the patient was called back for re-examination. There were no systemic signs or symptoms except for an enlarged right submandibular lymph node, which was removed. It showed reactive hyperplasia and no malignant tumour. One and a half months later the patient was found to have a recurrent epibulbar mass in the same quadrant, similar in size to the original tumour but several millimeters further back from the limbus (Fig 1). This was extensively resected the following day, and the same findings of malignancy were seen. Because of the known nature of this tumour, and in consultation with the Oncology Department, we decided to exenterate the right orbit. In five years of follow up there has been no evidence of recurrence or metastases.

Pathological findings. The specimen from the first excision consisted of a few pieces of partially pigmented soft tissue, the larger piece measuring 13×9×8 mm. The specimen from the second excision consisted of two pieces of soft tissue, the larger measuring 7×5·5×3 mm and coated by some pigment. In cut section the tissue was homogeneously white.

Microscopic examination of both excisional biopsies revealed malignant cells showing striking pleomorphism and many mitotic figures (Fig 2). There were small round cells as well as very large cells and multinucleated giant cells. Most of their nuclei had one or more nucleoli. Many foamy cells with granular nuclei were seen (Fig 3). A fascicular pattern was observed in areas of the tumour. Immunohistochemical studies with the peroxidase-antiperoxidase technique (PAP) staining showed positive staining of many tumour cells for lysosome and vimentin

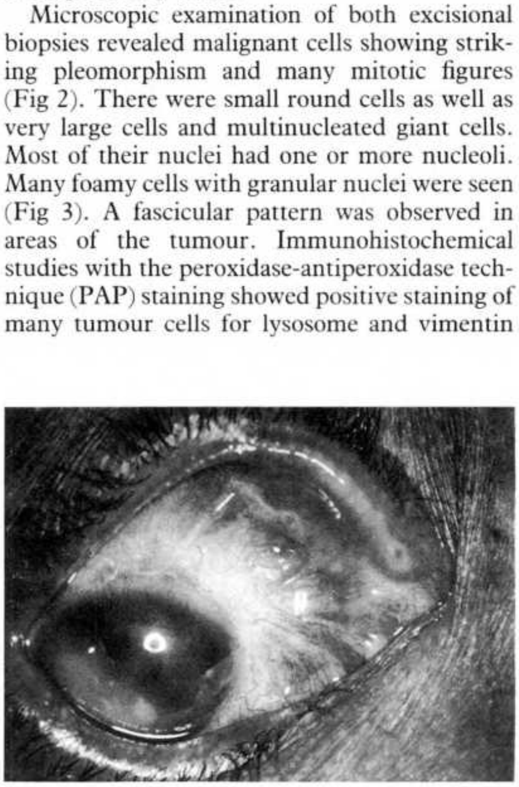


Figure 1 The right eye of case 1 presenting a recurrent epibulbar mass in the superonasal quadrant.

Hadassah University Hospital, Jerusalem, Israel
Department of Ophthalmology
J Pe'er
S Levinger
M Ilsar

Department of Pathology
E Okon

St John Ophthalmic Hospital, Jerusalem
H Climenhaga

Correspondence to:
Dr J Pe'er, Department of Ophthalmology, Hadassah University Hospital, PO Box 12000, 91120 Jerusalem, Israel.

Accepted for publication
11 May 1990

*Presented at the 11th Biannual Meeting Washington, DC, June 1985, and the 13th Biannual Meeting of the AOA-AFIP, Washington, DC, June 1989.

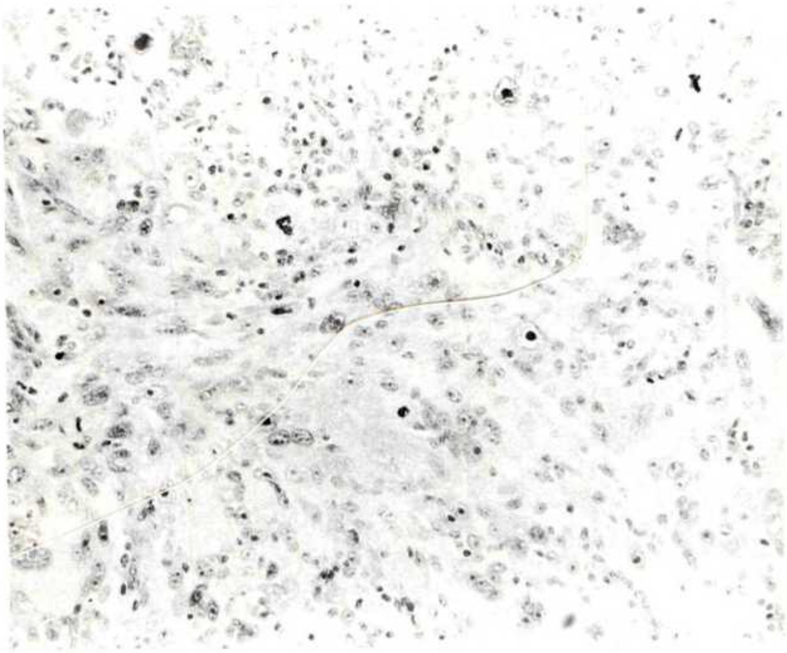


Figure 2 Case 1 shows a malignant pleomorphic soft tissue tumour with many mitotic figures and large giant cells (in left lower corner). (Haematoxylin and eosin, ×183.)

and negative staining for S-100 protein and cytokeratin. The diagnosis was made of MFH, pleomorphic type.

The exenteration specimen measured 38×39×39 mm, and included the right eyeball, orbital contents, and eyelids. The optic nerve, 4 mm in length, was attached. There was a symblepharon of the upper fornix of the conjunctiva which was occupied by a whitish shallow mass. The cornea was partially opaque. The specimen was dissected vertically.

Microscopic examination of the exenteration specimen showed a section through the medial part of an eye globe and its adnexa. There were no remarkable finding in the eye. The conjunctiva showed chronic inflammatory infiltration. The conjunctival and eyelid tissue superior to the upper conjunctival fornix was massively infiltrated by chronic inflammatory cells and bizarre pleomorphic tumour cells, many of them with foamy cytoplasm. Some of them were multinucleated giant cells, identical to the cells found in the previous excisional biopsies. The borders of the exenteration specimen were free of tumour.

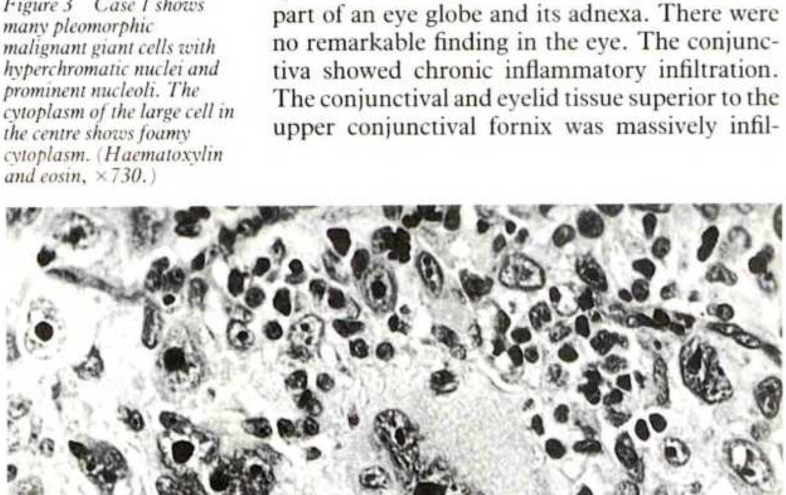


Figure 3 Case 1 shows many pleomorphic malignant giant cells with hyperchromatic nuclei and prominent nucleoli. The cytoplasm of the large cell in the centre shows foamy cytoplasm. (Haematoxylin and eosin, ×730.)

Formalin-fixed tumour tissue was processed for electron microscopy. The tissues were fixed in 2% glutaraldehyde buffered in phosphate-saline buffer (0·1 M; pH 7·2) and postfixed in 1% OsO_4 for one hour. After dehydration in graded ethanol the specimens were embedded in Spurr resin. Ultrathin sections of approximately 70 nm were collected on 300 mesh copper grids and contrasted with uranyl and lead citrate. The sections were examined with a Philips EM300 operating at 60 kV.

The electron microscopic studies showed in both types of cells the histiocytic as well as the fibroblasic variants, lipid cisternae as well as lysosomes. Dilated cisternae of rough-surfaced endoplasmic reticulum containing electron-dense granular material were also found (Fig 4). In some areas broken parts of rough-surfaced endoplasmic reticulum were seen.

CASE 2

A 3½-year-old girl presented to the Eye Clinic at Kamuzo Central Hospital in Lilongwe, Malawi, in February 1988 with tumours in both eyes. The mother was over 40 years old and the father was not known. One sister and two brothers were healthy. The child's birth had been normal, but her development had been slow. A few months after her birth the mother noticed 'changes' and, later, tumours on the child's exposed skin. There were no similar findings in other known family members. The girl was diagnosed as suffering from xeroderma pigmentosum.

Examination of the girl revealed microcephaly and mental retardation. The girl walked but did not speak. The skin of the face, including the eyelids, showed atrophic changes, pigmentation, depigmentated areas, and multiple tumours (Fig 5). Similar tumours were seen to a less extent on the neck, hands, and feet.

Examination of the left eye revealed a tumour of the bulbar conjunctiva. The cornea was not involved in the tumour but was hazy and partially vascularised. The right eye showed a large tumour of the bulbar conjunctiva with involvement of the cornea (Fig 5). A skin tumour was also noted on the upper lid. The intraocular structures could not be checked, and it was impossible to assess her visual acuity.

The tumours of the eyes were removed, and those of the skin were shaved. All specimens were sent to our laboratory for histopathological evaluation. The child was lost to follow-up.

The conjunctival corneal tumour of the right eye consisted of a brown piece of tissue measuring 12×10×7 mm.

Microscopic examination revealed a tumour with striking pleomorphism, with many abnormal mitotic figures and areas with fascicular pattern of the cells (Fig 6). There were many large bizarre cells and multinucleated giant cells (Fig 7). Many of the cells showed foamy cyto-

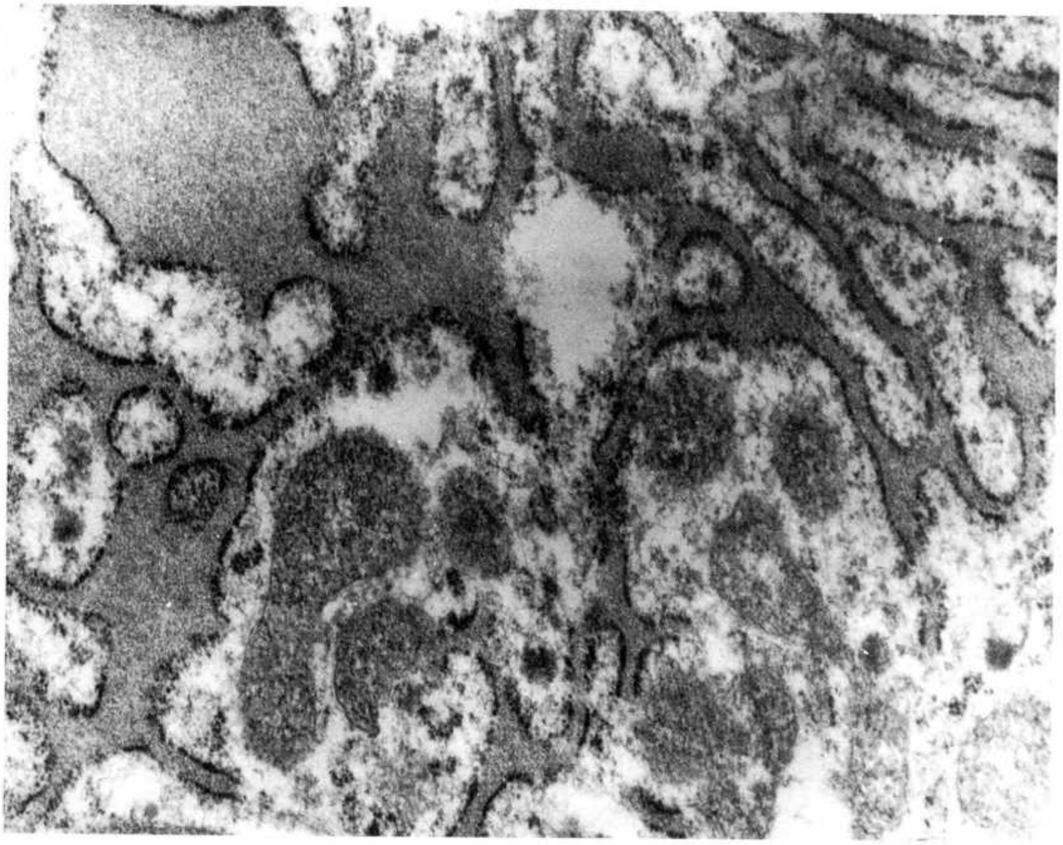


Figure 4 Case 1 electron microscopic examination reveals dilated cisternae of rough-surfaced endoplasmic reticulum with electron-dense granular material. (Haematoxylin and eosin, ×60 000.)

plasm. The tumour was infiltrated by inflammatory cells.

Immunohistochemical studies were positive for vimentin and lysozyme but negative for S-100 protein and cytokeratin.

Discussion

Malignant fibrous histiocytoma represents one of the commonest soft tissue tumours[19 20] and can occur in practically every part of the body.[19-21] These tumours show a remarkable tendency to metastasise to regional lymph nodes in addition to spreading by the blood stream.[19-21] Their local aggressiveness is proved by their extremely high rate of local recurrence (100% in one series)[19 20] when only limited excisions are performed. Therefore radical surgery is indicated in their treatment.[20] Although MFH superficially situated in the subcutis is considered to have better prognosis than deeper tumours, there is no experience with MFH of the conjunctiva. These facts led us in case 1 to exenterate the whole orbital contents to the periosteum.

Other clinical features of our patient (case 1) are in accordance with those of most patients with MFH at other sites.[18] The male sex is predominant, and the age distribution is from the third to the sixth decade. In addition the main histological features of MFH which were found in our case were comparable to those of MFH found elsewhere in the body.[20]

Case 2 is the first reported of xeroderma pigmentosum with MFH of either the skin or conjunctiva. Most of the neoplastic tumours in these cases are of epithelial origin, such as squamous cell carcinoma and basal cell carcinoma, or of melanocytic origin, such as malignant melanoma, which can be explained by the exposure of the skin cells to ultraviolet radiation. Soft tissue tumours in xeroderma pigmentosum are extremely rare, and only a few fibrosarcomas and angiomas of the skin have been described.[22]

Xeroderma pigmentosum occurs more commonly in whites, but in blacks the disease displays more severe ocular pathology and less severe skin involvement,[22-24] probably because of the protective effect of the pigmented skin.

Ocular symptoms in xeroderma pigmentosum occur in up to 80% of the patients, and are

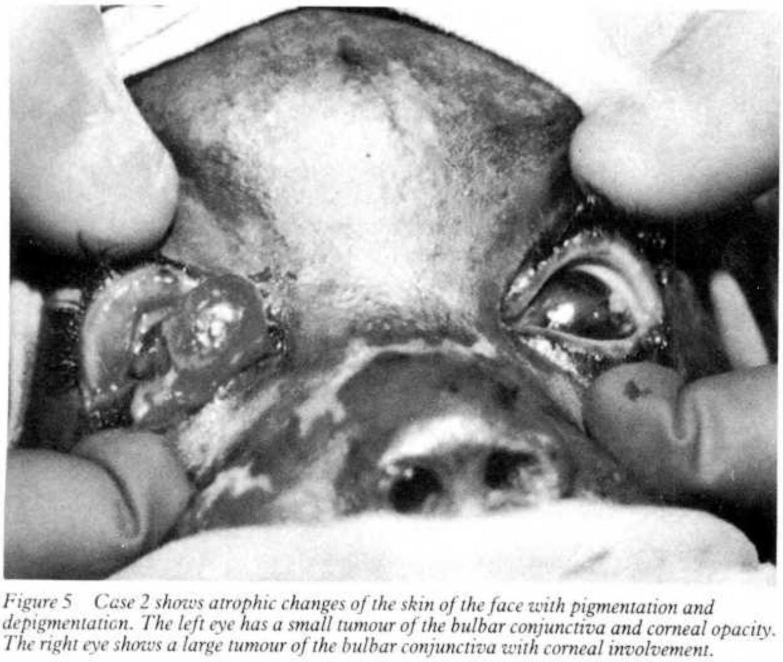


Figure 5 Case 2 shows atrophic changes of the skin of the face with pigmentation and depigmentation. The left eye has a small tumour of the bulbar conjunctiva and corneal opacity. The right eye shows a large tumour of the bulbar conjunctiva with corneal involvement.

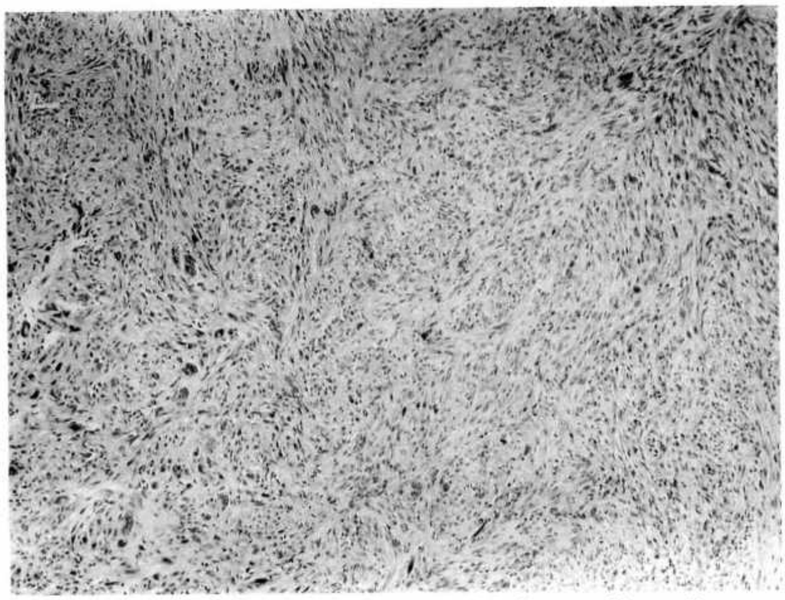


Figure 6 Case 2 shows a tumour with fascicles of spindled cells arranged in a storiform pattern. (Haematoxylin and eosin, ×73.)

confined to the eyelids and anterior segment of the globe.[25] Photophobia may start as early as age 2 years. The eyelids, especially the lower, may show atrophy of the skin, progressive madarosis, scarring, entropion, ectropion, trichiasis, lagophthalmos, symblepharon, ankyloblepharon, and sometimes loss of the entire lower lid substance. Basal cell carcinoma occurs frequently. Conjunctival findings may include hyperaemia, xerosis, oedema, mucoid exudates, keratinisation, hyperpigmentation, atrophy, pinguecula, and pseudopterygial changes and frank malignancies. The limbus is preferentially involved, especially in the interpalpebral zone. The cornea is frequently affected by vascularisation, opacification, and recurrent ulceration. Corneal or conjunctival-corneal neoplasms may occur. Inflammation of the iris may result in atrophy, abnormal pigmentation, and synechiae. No characteristic alterations of the lens or fundus are seen.[25]

In the largest survey of xeroderma pigmentosum, ocular neoplasms, apart from neoplasms of eyelids, were found in 11% of the patients.[25] Neoplasms occurred most frequently at the limbus, followed by the cornea and conjunctiva. The most frequent histological type reported was squamous cell carcinoma, followed by basal cell carcinoma. There have been reports of five patients with ocular melanoma, including one with uveal tract melanoma.[6 26]

Originally thought to arise from histiocytes and 'facultative' fibroblasts, MFH is now accepted as originating from a primitive mesenchymal cell with a capacity to differentiate along either or both cell lines.[20 21] Immunohistochemical studies[27] and an ultrastructural analysis[28] of these tumours have raised questions about their histiocytic nature, and this subject is controversial. While one immunohistological study[29] suggests that proliferating cells in MFH are of a histiocytic nature, other studies[30-32] have raised the possibility that they are primarily fibroblastic in nature.

The markedly pleomorphic, highly malignant histological appearance of the tumours has caused us, as well as our consultants, difficulties in diagnosis. We considered in our differential diagnosis malignant melanoma with an unusual degree of cellular pleomorphism, as well as a bizarre kind of carcinoma. Immunohistochemical studies that were positive for lysosome and vimentin and negative for S-100 protein and cytokeratin helped us to rule out the possibility of malignant melanoma or carcinoma and led us to the final diagnosis.

The electron microscopic findings of lipid vacuoles, lysozymes, and broken, rough endoplasmic reticulum were described and discussed in a previous report of benign FH of the conjunctiva.[6] Our findings of a very dilated, rough surfaced, endoplasmic reticulum, which contained granular material, were described in two cases of MFH of the orbit.[18] The role of electron microscopic studies in MFH has been discussed,[20] and the authors concluded that there are no ultrastructural features which are specific for MFH: cells with similar characteristics can be found in other soft tissue tumours. The electron microscopic study is only an ancillary or confirmatory procedure in the diagnosis of MFH.

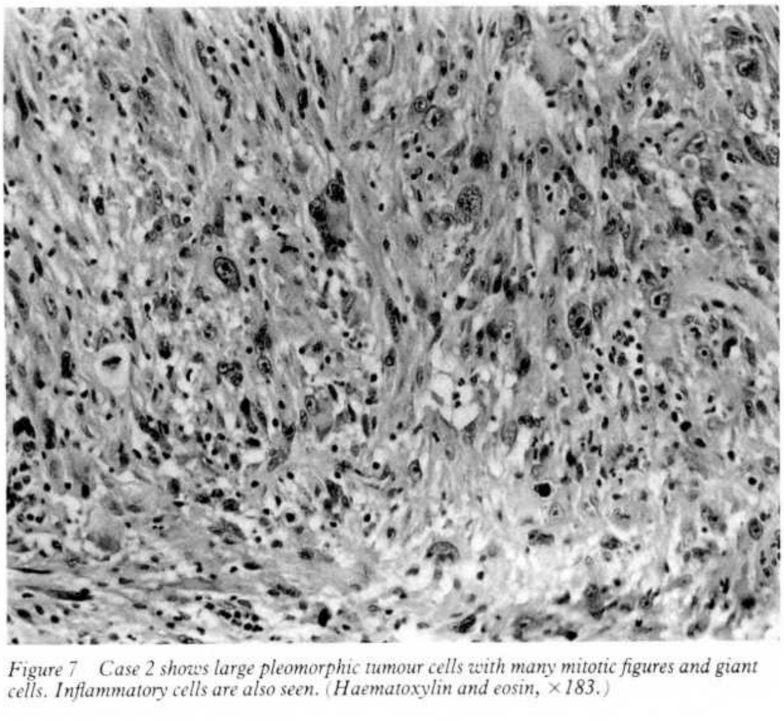


Figure 7 Case 2 shows large pleomorphic tumour cells with many mitotic figures and giant cells. Inflammatory cells are also seen. (Haematoxylin and eosin, ×183.)

1 Albert DM, Smith RS. Fibrous xanthomas of the conjunctiva. *Arch Ophthalmol* 1968; **80**: 874–9.
2 Jakobiec FA. Fibrous histiocytoma of the corneoscleral limbus. *Am J Ophthalmol* 1974; **78**: 700–6.
3 Flaudi JE, Kenyon K, Green WR. Fibrous histocytoma of the corneoscleral limbus. *Am J Ophthalmol* 1975; **80**: 619–24.
4 Elsas FJ, Green WR. Epibulbar tumors in childhood. *Am J Ophthalmol* 1975; **79**: 1001–7.
5 Paglen PG, Karcher DS, McMahon RT. Fibrous histiocytoma of the conjunctiva. *Ann Ophthalmol* 1980; **12**: 522–5.
6 Iwamoto T, Jakobiec FA, Darrell RW. Fibrous histiocytoma of the corneoscleral limbus. *Ophthalmology* 1981; **88**: 1260–8.
7 Lahoud S, Brownstein S, Laflamme MY. Fibrous histiocytoma of the corneoscleral limbus and conjunctiva. *Am J Ophthalmol* 1988; **106**: 579–83.
8 Kantelip B, Nores JM, Boccard R, Souoedan M, Bacin F. Un cas d'histiocytome fibreux de la conjonctive. *Presse Med* 1988; **17**: 859–61.
9 Litricin O. Fibrous histiocytoma of the corneosclera. *Arch Ophthalmol* 1983; **101**: 426–8.
10 Lew HR, Sheppard CL. Variations in management of adnexal tumors. *Aust NZ J Ophthalmol* 1985; **13**: 189–91.
11 Delgado-Partida P, Rodriguez-Trujillo F. Fibrosarcoma

(malignant fibrosarcoma) involving conjunctiva and ciliary body. *Am J Ophthalmol* 1972; 74: 479–85

12 Urdiales-Viedma M, Moreno-Prieto M, Martos-Padilla S. Pleomorphic fibrous histiocytoma of the corneoscleral limbus *Am J Ophthalmol* 1983, 95: 560–1

13 Margo CE, Horton MB Malignant fibrous histiocytoma of the conjunctiva with metastasis. *Am J Ophthalmol* 1989, 107: 433–4

14 Doxanas MT; Green WR, Arentsen JJ, Elsas, FJ Lid lesions of childhood a histologic survey at the Wilmer Institute (1923–1974) *J Pediatr Ophthalmol Strabismus* 1976, 13: 7–39

15 Harashina T, Maruyama Y, Kitamura K The trilobed flap *Plast Reconstr Surg* 1977; 60: 623–4

16 Jakobiec FA, DeVoe AG, Boyd J Fibrous histiocytoma of the tarsus *Am J Ophthalmol* 1977; 84: 794–7

17 John T, Yanoff M, Scheie HG Eyelid fibrous histiocytoma *Ophthalmology* 1981; 88: 1193–5.

18 Font RL, Hidayat AA. Malignant fibrous histiocytoma of the orbit. A clinicopathologic study of 150 cases. *Hum Pathol* 1982, 13: 195–209

19 Laties R Malignant fibrous histiocytoma A review article *Am J Surg Pathol* 1982, 6: 761–7.

20 Weiss SW. Malignant fibrous histiocytoma. A reaffirmation *Am J Surg Pathol* 1982; 6: 773–84

21 Lattes R, ed *Tumors of the soft tissues (atlas of tumor pathology series)* AFIP; 1982. 130–46

22 Kraemar K, Lee MM, Scotto J Xeroderma pigmentosum Cutaneous, ocular and neurologic abnormalities in 830 published cases *Arch Dermatol* 1987, 123: 241–50.

23 Bellows RA, Lahav M, Lepreau FJ, Albert DM Ocular manifestations of xeroderma pigmentosum in a black family *Arch Ophthalmol* 1974, 92: 113–7

24 Freedman J Corneal transplantation with associated histopathologic description in xeroderma pigmentosum occurring in a black family *Ann Ophthalmol* 1979, 11: 445–50

25 Stenson S Ocular findings in xeroderma pigmentosum. Report of two cases *Ann Ophthalmol* 1982, 14: 580–5.

26 Kitogawa K, Oishi T, Inoue M. Choroidal malignant melanoma occurring in a patient with xeroderma pigmentosum *Folia Ophthalmol Jpn* 1981, 32: 657–63.

27 du Boulay CEHA. Demonstration of antitrypsin and antichymotrypsin in fibrous histiocytomas using the immunoperoxidase technique. *Am J Surg Pathol* 1982; 6: 559–64

28 Hoffman MA, Dickearsin GR Malignant fibrous histiocytoma An ultrastructural study of eleven cases. *Hum Pathol* 1983, 14: 913–22

29 Inoue A, Aozasa K, Tsujimoto M, Tamai M, Chatani F, Ueno H. Immunohistological study of malignant fibrous histiocytoma *Acta Pathol Jpn* 1983; 34: 759–65.

30 Wood GS, Beckstead JH, Tuner RR, *et al.* Malignant fibrous histiocytoma tumor cells resemble fibroblasts. *Am J Surg Pathol* 1986; 10: 323–35.

31 Brecher ME, Wilbur HF Absence of mononuclear phagocyte antigens in malignant fibrous histiocytoma *Am J Clin Pathol* 1986, 86: 344–8.

32 Roholl PJM, Kleyne J, Van Unnite JAM. Characterization of tumor cells in malignant fibrous histiocytoma and other soft tissue tumors in comparison with malignant histiocytes. *Am J Pathol* 1985, 121: 269–74.

A case of cerebrotendinous xanthomatosis II: the sterol content of a cataractous lens

P McKenna, S J Morgan, R C Bosanquet, M F Laker

Abstract

The cholestanol content of a cataractous lens nucleus from a patient with cerebrotendinous xanthomatosis (CTX) was quantified by gas chromatography-mass spectrometry and found to be 0·27 μg per mg freeze-dried lens tissue. The cholestanol-cholesterol ratio of 1·7% in the lens nucleus was similar to that in the serum of the CTX patient. The cholestanol content and cholestanol-cholesterol ratio in the CTX lens were approximately four-fold and six-fold greater respectively than the mean levels found in three senile cataractous lens nuclei analysed simultaneously for comparative purposes.

Department of Clinical Biochemistry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP
P McKenna
M F Laker

Department of Ophthalmology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE
S J Morgan
R C Bosanquet

Correspondence to: Dr P McKenna, Department of Clinical Chemistry, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

Accepted for publication 11 May 1990

Cerebrotendinous xanthomatosis (CTX) is caused by a rare inborn error of bile acid synthesis.[1] Its main clinical features include cataracts, tendon xanthomata, and neurological abnormalities, which usually first become apparent during the second and third decades of life.[2] The biochemical defect lies in hydroxylation of the steroid side-chain of cholesterol (5-cholesten-3β-ol), prior to oxidative cleavage, which occurs during hepatic conversion to cholic and chenodeoxycholic acids (Fig 1).[1] The consequent reduced level of the latter bile acid (cholic acid can be synthesised by an alternative minor pathway) decreases the negative feedback inhibition on the rate-limiting enzymes for cholesterol and bile acid synthesis, namely, 3-hydroxy-3-methylglutaryl CoA reductase and cholesterol 7 α-hydroxylase respectively.[3,4] This results in increased hepatic synthesis of cholesterol and bile acid precursors.[5] Otherwise minor side-products of the bile acid pathway such as cholestanol (5 α-cholestan-3β-ol) and 'bile alcohols' (cholesterol derivatives hydroxylated on the steroid nucleus and side-chain without side chain cleavage) are also synthesised in increased amounts.[1,5] There is increased biliary secretion of cholestanol and 'bile alcohol' glucuronides, raised serum levels of cholestanol, but not serum cholesterol, and excessive cholestanol and cholesterol deposition in tissues.[1,6,7]

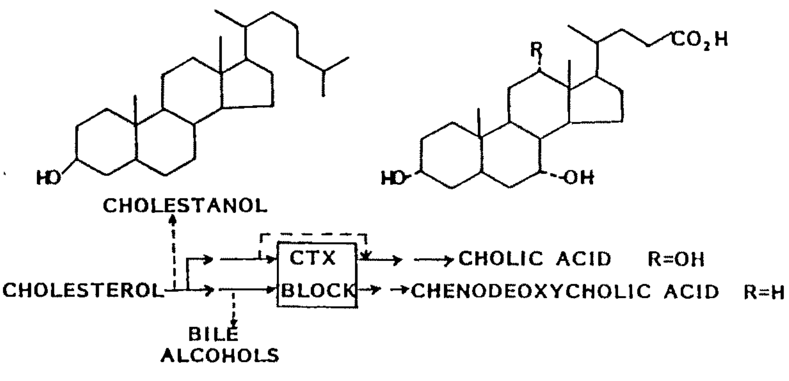


Figure 1 Bile acid pathway in CTX.

Sterol deposition is widespread, with xanthomata in the cerebellum and forebrain as well as in tendons; raised cholestanol levels have been found in virtually every tissue examined.[2,7,8] An earlier report of the cholestanol content of a cataractous lens from a CTX patient describes the cholestanol content as 'significantly elevated'.[9] Others, however, have reported that cholesterol is the only sterol found in human cadaver lens and senile cataract.[10]

The aim of this study was to quantify the cholestanol content in a cataractous lens nucleus of a CTX patient. A case report giving full details has been published.[11] The clinical features were typical of CTX, and although bilateral cataracts were not recorded until the age of 40 years, the patient was first prescribed spectacles at 21, when his best corrected visual acuity was 6/18 in each eye. One year after his second cataract extraction with intraocular lens insertion his visual acuities were 6/6 part right, 6/6 left compared with preoperative acuities of 2/60 and 4/60 respectively.

Material and methods

Left lens extracapulsar cataract extraction was performed on the 42-year-old male CTX patient. Three senile cataractous lens nuclei from male patients in the eighth decade (mean age 77 years) were also obtained following extracapsular extraction. The nuclei were stored at −70°C under nitrogen until analysed simultaneously. Immediately prior to analysis the nuclei were freeze-dried to obtain a representative weight. The total lipid content of each nucleus was extracted by the Folch procedure.[12] The subsequent steps were performed in duplicate. The free sterols were obtained by saponification of a known amount (approximately 20%) of the lipid extract. Cholestane, added prior to saponification, was used as an internal standard. The free sterols were analysed by gas chromatography-mass spectrophotometry (GC-MS) in the selective ion quantitative mode,[13] monitoring peaks with mass-charge ratio of 388, 386, and 372 (molecular weights of cholestanol, cholesterol, and cholestane are 388, 386, and 372 respectively).

Standards were prepared from known amounts of cholestanol and a fixed amount of cholesterol and cholestane subject to the same saponification procedure. A standard curve was plotted relating the cholestanol content of the standard samples to the cholestanol/cholestane area ratio. The amount of cholestanol in the lens nucleus samples was estimated from this standard curve by means of the calculated cholestanol/cholestane ratio of the unknown lens sample. The free sterol peaks, but not internal standard, overlapped in the gas chromatography trace. Because of this the cholestanol component was estimated from the GC-MS peak with mass-charge ratio of 388 after compensation for the cholesterol component. The cholesterol component of the peak at 388 was calculated from the peak at 386 by means of the ratio

Table 1 The sterol content of cataractous lens nuclei

	CTX	*Senile*
Total cholestanol content per lens	13 1 μg	2·8 μg
Cholestanol content per mg freeze-dried mass of lens	0·27 μg	0·07 μg
Cholestanol/cholesterol ratio	1·7%	0·3%

Table 2 Serum sterol values from the CTX patient

Cholestanol	93 μmol/l (<10)
Cholestanol/cholesterol ratio	1·5% (<0·2%)

Reference values for normal serum in parentheses.

obtained from cholestanol-free standards. The cholestanol-cholesterol mass ratio was calculated from the peak ratio after calibration with standard samples of known cholestanol and cholesterol mass

Results

The sterol content of the CTX lens nucleus is shown in Table 1 together with the mean values of three senile lens nuclei for comparative purposes (in the absence of reference values). Corresponding serum values are given in Table 2.

The lens nucleus from the CTX patient had approximately a four-fold greater cholestanol content (corrected for freeze-dried lens nucleus mass) compared with the senile lens nuclei in which cholestanol was also detected. The cholestanol/cholesterol ratio in the CTX lens nucleus was similar to that in the serum of the CTX patient, but approximately six-fold greater than in the senile lens nuclei. The amount of cortex attached to the lens nuclei might differ between patients owing to the nature of the extracapsular extraction procedure; it is unlikely to influence the results significantly.

Discussion

It is likely that the cholestanol found in the lens nuclei in the senile cataracts and in the cataract secondary to CTX has an exogenous origin. The source of the cholestanol in both the CTX and senile cataracts is probably hepatic; the bile acid pathway is not known to occur in extrahepatic sites. Although cholestanol is present in the human diet, it is found only at very low levels (estimated at 0·1% of cholesterol) and is not well absorbed into the body.[2] Serum lipoproteins poorly penetrate aqueous humour,[14] but the similarity of the lens and serum cholestanol content suggest that cholestanol is deposited in the lens by equilibration from serum. The low levels of serum high density lipoprotein typically found in CTX patients may also inhibit sterol removal from peripheral tissues,[2 15] but this is of unknown significance in relatively isolated tissues such as the lens.

Whether cholestanol has a role in the mechanism of cataractogenesis is unclear. Other cholesterol derivatives, such as 20,25-diazacholesterol and 3-β (2-diethylaminoethoxy)-androst-5-en-17-one hydrochloride, which also are inhibitors of cholesterol synthesis, have been shown to be cataractogenic in experimental animals.[16 17] Triparanol, a non-steroidal inhibitor of cholesterol synthesis, also causes cataract formation in man.[18] One mechanism of cataractogenesis by such agents has been postulated to be mediated via alterations in intracellular electrolyte concentrations in the lens and subsequent effects on lens proteins, especially γ-crystallins.[17] Although cholestanol is not an inhibitor of cholesterol synthesis, incorporation of cholestanol in the lens cellular membranes, partially replacing cholesterol, might cause a functional defect equivalent to cholesterol deficiency. Thus in lens tissue, which is critically isolated from systemic cholesterol metabolism, such a functional deficit might activate the same mechanisms leading to cataractogenesis as those previously postulated for direct inhibition of cholesterol synthesis.[17]

It can therefore be concluded that there is excess deposition of cholestanol in the nucleus of the CTX lens in association with premature cataract formation. In the light of cataractogenesis by other agents this suggests, but does not prove, a causative role for cholestanol. If cholestanol has an aetiological role, a general mechanism for cataractogenesis could be postulated based on interference with cholesterol function, possibly an alteration in cell membrane permeability rather than cholesterol deficiency itself.

1 Setoguchi T, Salen G, Tint GS, Mosbach EH. A biochemical abnormality in cerebrotendinous xanthomatosis: impairment of bile acid biosynthesis associated with incomplete degradation of the cholesterol side chain. *J Clin Invest* 1974; 53: 1393–401

2 Salen G, Shefer S, Berginer VM Familial diseases with storage of sterols other than cholesterol· cerebrotendinous xanthomatosis and sitosterolaemia with xanthomatosis In. Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds. *The metabolic basis of inherited disease* 5th ed. New York McGraw-Hill, 1983: ch 34. 713–30

3 Nicolau G, Shefer S, Salen G, Mosbach EH. Determination of hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity in man *J Lipid Res* 1974; 15: 94–8.

4 Nicolau G, Shefer S, Salen G, Mosbach EH Determination of hepatic cholesterol 7α-hydroxylase activity in man *J Lipid Res* 1974, 15: 146–51

5 Salen G, Grundy SM. The metabolism of cholestanol, cholesterol and bile acids in cerebrotendinous xanthomatosis *J Clin Invest* 1973, 52: 2822–35

6 Salen G Cholestanol deposition in cerebrotendinous xanthomatosis a possible mechanism *Ann Intern Med* 1971. 75: 843–51.

7 Menkes J, Schimschock JR, Swanson PD. Cerebrotendinous xanthomatosis· the storage of cholestanol within the nervous system *Arch Neurol* 1968; 19: 47–53.

8 Philippart M, van Bogaert L Cholestanolosis (cerebrotendinous xanthomatosis): a follow-up study on the original family. *Arch Neurol* 1969; 21: 603–10

9 Seland JH, Slagsvold JE The ultrastructure of lens and iris in cerebrotendinous xanthomatosis *Acta Ophthalmol (Kbh)* 1977; 55: 201–7.

10 Cotlier E, Obara Y, Toftness B Cholesterol and phospholipids in protein fractions of human lens and senile cataract *Biochem Biophys Acta* 1978; 530: 267–78.

11 Morgan SJ, McKenna P, Bosanquet RC A case of cerebrotendinous xanthomatosis I Unusual ophthalmic features *Br J Ophthalmol* 1989; 73: 1011–4.

12 Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues *J Biol Chem* 1957; 226: 497–509.

13 Seyama Y, Ichikawa K, Yamakawa T. Quantitative determination of cholestanol in plasma with mass fragmentography. *J Biochem* 1976; 80: 223–8.

14 Cenedella RJ. Lipoproteins and lipids in cow and human aqueous humour *Biochim Biophys Acta* 1984; 793: 448–54

15 Shore V, Salen G, Cheng FW, *et al.* Abnormal high density lipoproteins in cerebrotendinous xanthomatosis *J Clin Invest* 1981, 68: 1295–304.

16 Peter JB, Andiman RM, Bowman RL, Nagatomo T Myotonia induced by diazacholesterol: increased (Na^++ K^+)–ATPase activity of erythrocyte ghosts and development of cataracts *Exp Neurol* 1973, 41: 738–44.

17 Cenedella RJ, Bierkamper GG. Mechanism of cataract production by 3-β(2-diethylaminoethoxy) androst-5-en-17-one hydrochloride, U18666A an inhibitor of cholesterol biosynthesis. *Exp Eye Res* 1979; 28: 673–88

18 Laughlin RC, Carey TF Cataracts in patients treated with Triparanol. *JAMA* 1962; 181: 339–40.

British Journal of Ophthalmology, 1990, **74**, 631–634

Histology of the lens in the Weill-Marchesani syndrome

Hisako Fujiwara, Yasushi Takigawa, Shinya Ueno, Kanshi Okuda

Department of Ophthalmology, Kawasaki Hospital, Kawasaki Medical School
H Fujiwara
Y Takigawa

Department of Ophthalmology, Tsuyama Central Hospital
S Ueno

Department of Ophthalmology, National Okayama Hospital, Japan
K Okuda

Correspondence to:
Dr Hisako Fujiwara,
Department of Ophthalmology, Kawasaki Hospital, Kawasaki Medical School, 2–1–80 Nakasange, Okatama 700, Japan.

Accepted for publication
26 April 1990

Abstract

The Weill-Marchesani syndrome is a rare systemic connective tissue disease characterised by small stature, brachydactyly, ectopia lentis, and spherophakia. Three siblings with typical manifestations of this syndrome were reported. The ophthalmological findings in all these cases were spherophakia, severe myopia, a shallow anterior chamber, and narrow angle glaucoma. Two cases underwent laser iridotomy and drug treatment. In the third case the lens was removed from the eye because of injury, and this lens was examined by light and electron microscopy.

The Weill-Marchesani syndrome was first reported in one patient with brachydactyly and microspherophakia by Weill[1] in 1932 during research on the Marfan syndrome. In 1936 Marchesani[2] reported four cases with brachycephaly, small stature, brachydactyly, and microspherophakia considered to have this syndrome.

The Weill-Marchesani syndrome is characterised by dystrophia mesodermalis hyperplasia in contrast to the Marfan syndrome, in which dystrophia mesodermalis hypoplasia is present.[3] The Weill-Marchesani and Marfan syndromes therefore appear to be mirror images of each other.[4]

In this syndrome treatment of the glaucoma is the main problem.

Three siblings with typical manifestations of the syndrome are reported on here. Two underwent laser iridotomy and drug treatment to control the intraocular pressure. In the third case the lens had been removed from the eye because of injury, and this lens was examined histologically.

Case reports

Case 1, proband, a 13-year-old female (Figs 1, 2) and case 2 eldest brother of case 1, 30-year-old male (Fig 3) were typical cases, successfully treated by laser iridotomy.

Case 3 was a 20-year-old male, elder brother of case 1. Because his sister and brother had been treated for glaucoma he came to the authors' department for a detailed examination. His visual acuity was 20/20 with −11D in the right eye and 24/20 with −14D in the left eye. The anterior chamber was shallow and the angle was narrow. The intraocular pressure was 14 mmHg in the right eye and 16 mmHg in the left.

At 1800 on 3 June 1988 a piece of wood struck him in the right eye while he was cutting down a tree with an electric saw. He was immediately examined by a local physician and underwent an emergency operation because of a ruptured right eyeball. The lens was easily removed from the eye during operation. The details of Zinn's zonule were not clear. The lens capsule was not ruptured and spherophakia was observed. The equatorial diameter was rather small at 7 mm, and the sagittal diameter was longer than normal. There was some protrusion in the pupillary area (Fig 4).

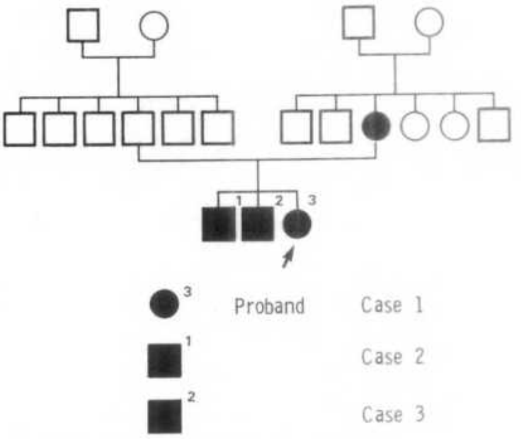


Figure 1 Family tree of patients reported on here.

The lens was immediately fixed in neutral formalin.

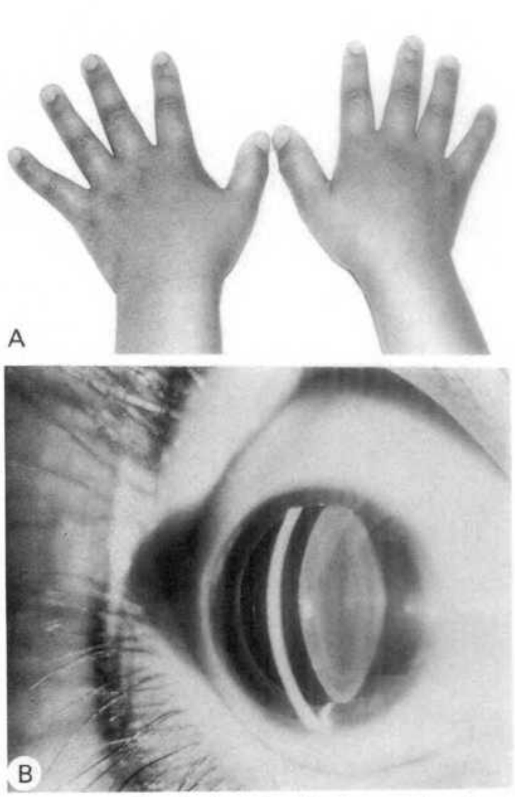


Figure 2 A: Short hands with stubby fingers of the proband. B: Right eye of the same patient showing microspherophakia.

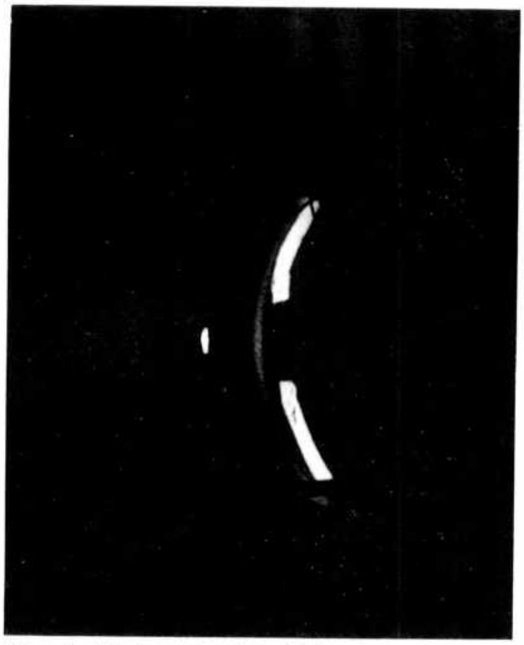


Figure 3 Slit-lamp view of the elder brother of the proband showing an extremely shallow anterior chamber.

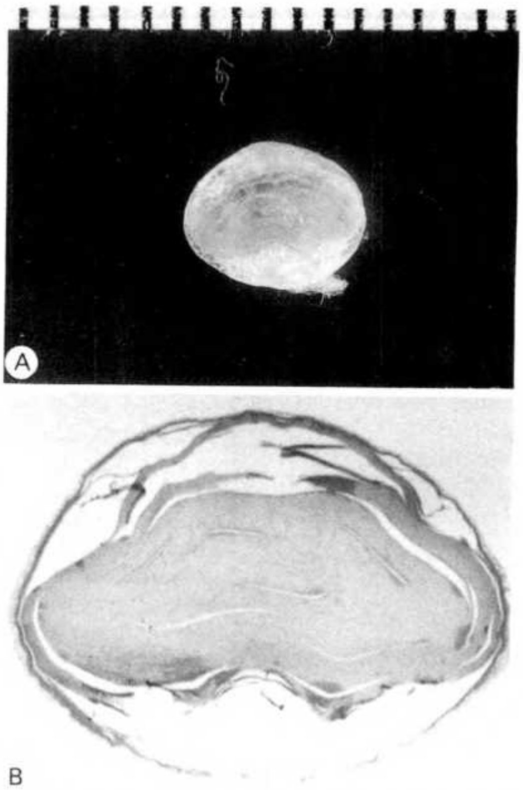


Figure 4 Extracted lens of the brother of the proband; small in size and round in shape. B: Appearance of the extracted lens. Large sagittal diameter and projection into the pupillary space are seen.

LIGHT MICROSCOPY

The anterior capsule appeared to be almost normal. The epithelial cells were irregularly shaped and some of their nuclei appeared pyknotic. Many vacuoles were seen between epithelial cells. Many of the cortical fibres had liquefied, forming homogeneous amorphous masses. The nuclear lens fibres were strongly eosinophilic and well orientated (Fig 5).

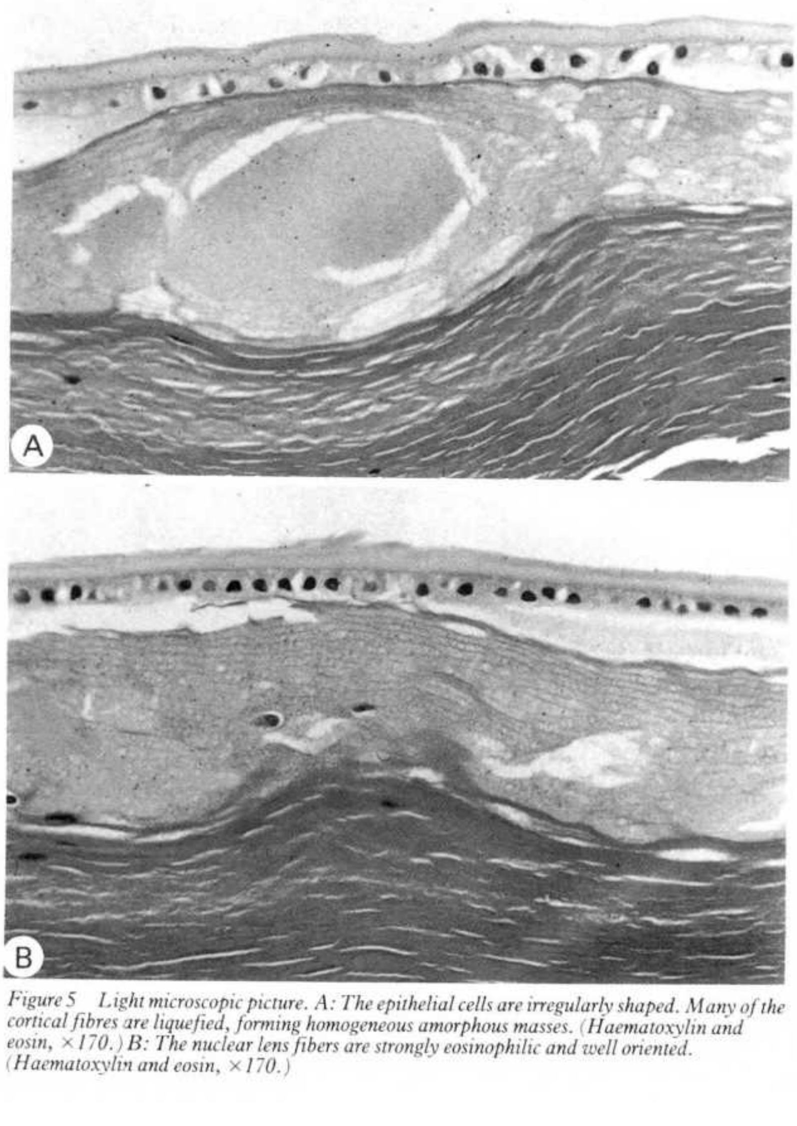


Figure 5 Light microscopic picture. A: The epithelial cells are irregularly shaped. Many of the cortical fibres are liquefied, forming homogeneous amorphous masses. (Haematoxylin and eosin, ×170.) B: The nuclear lens fibers are strongly eosinophilic and well oriented. (Haematoxylin and eosin, ×170.)

The anterior capsule stained strongly positive with periodic acid Schieff. A few cortical lens fibre nuclei remained in the deeper area (Fig 6).

The posterior capsule was thin. The subcapsular posterior cortex was totally liquefied, and homogeneous proteinaceous masses filled with subcapsular area (Fig 7).

ELECTRON MICROSCOPY

The anterior capsule was homogeneous and its anterior and posterior surfaces were smooth. The epithelial cells were mostly cuboid. The nucleus was round. The nuclear envelope was smooth, with many nuclear pores. The euchromatin was finely granular and evenly distributed throughout the nucleus, and the heterochromatin appeared as many dense, irregularly formed aggregates. In some degenerating cells nuclear envelopes were lost in some regions, and aggregates of heterochromatin had decreased in number. The cytoplasm contained small mitochondria, rough-surfaced endoplasmic reticulum, and single or aggregated ribosomes. Many vacuoles of different sizes were found throughout the cytoplasm. Adjacent cells often had deep interdigitations and showed many intercellular irregular gaps with fine granular debris. The subepithelial lens fibres were completely degenerated and appeared as evenly distributed granular masses (Figs 7, 8, 9).

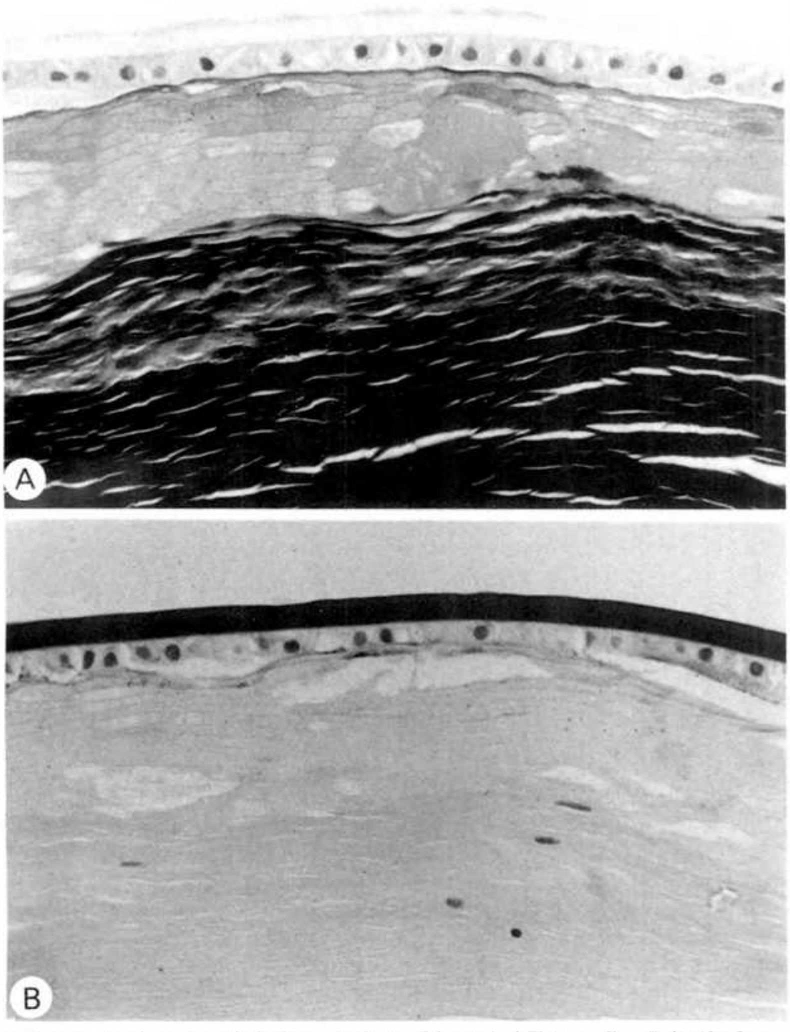


Figure 6 Light microscopic findings. A: Some of the cortical fibres are liquefied and a form homogeneous amorphous masses. The nuclear fibres are strongly eosinophilic. (Masson's trichrome, ×170.) B: The anterior capsule is strongly PAS-positive. (PAS, × 170.)

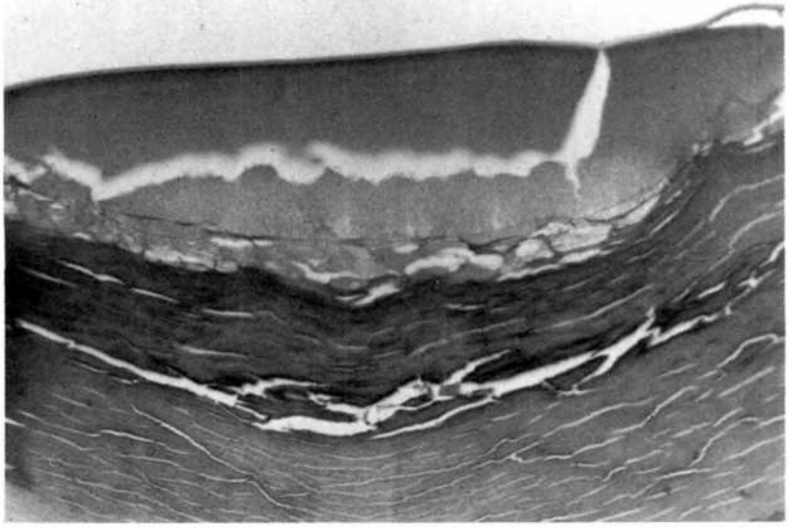


Figure 7 Posterior portion of the lens. The subcapsular posterior cortex is totally liquefied. (Masson's trichrome, ×170.)

Discussion

The ophthalmological complications of the Marchesani syndrome include microspherophakia associated with ectopia lentis, lens myopia, and secondary glaucoma. The lens is small and spherical with an equatorial diameter of 6·75 mm on the average and a sagittal diameter 25% larger than normal.[4] The angle becomes narrow because of the shallow anterior chamber caused by the spherophakia and the forward movement of the lens, but there have also been cases of congenital angular abnormalities.[5,6]

Peripheral iridectomy[7-9] is an operative technique for pupillary block glaucoma in this syndrome, but recently laser iridotomy has appeared as a safe method, with few complications.[10] Lensectomy is difficult to perform in these cases, and complications are apt to arise. However, it has been reported that no complications occur when irrigation-aspiration is performed with anterior capsulotomy by YAG laser.[11]

To maintain visual acuity an early diagnosis and surgery before the visual acuity decreases are necessary.[12] In the diagnosis of visual disturbances in children, cases have been reported in which attacks of acute glaucoma occurred from cyclopentolate eyedrops, or the glaucoma did not improve owing to pilocarpine eyedrops.[13]

Genetically this syndrome often involves autosomal recessive inheritance, and there have been cases where it appears in a father and his sons and daughters[14] and in a mother and sons.[15] In our report the syndrome appeared in a mother, her two sons, and a daughter. This case was considered to be one of autosomal dominant inheritance.

In the present study we obtained a lens removed from the eye owing to an accidental injury, and it was examined histologically. In previous reports there have been records only of the shape, size, and weight of the lens but no histological findings. It has been suggested that microspherophakia is caused by growth of the lens ceasing congenitally when the fetus is 5–6 months old, so that the lens retains it initial shape.[16] In the lens we obtained there was marked degeneration of the epithelial cells of the lens and marked liquefaction and destruction of the subcapsular cortical fibres in the anterior and posterior poles in addition to microspherophakia. These findings indicated a lens with a complicated cataract.[17] However, there was no hypertrophy of the capsule such as that seen in cataract lenses complicated with iriditis.

Degeneration and necrosis of the epithelial cells of the lens are caused by various factors including aging, inflammation, trauma, and surgery.[18] Destruction of the cortical fibres is a common histological change seen in lenses with senile cortical cataracts; in the present case of Weill-Marchesani syndrome it was considerable.

These changes appear to be due to physical and mechanical factors, because the lens is highly movable and often in contact with the iris, especially in association with long term irritation in the pupillary area in cases of microspherophakia. However, other biochemical changes within the lens cannot be ruled out.

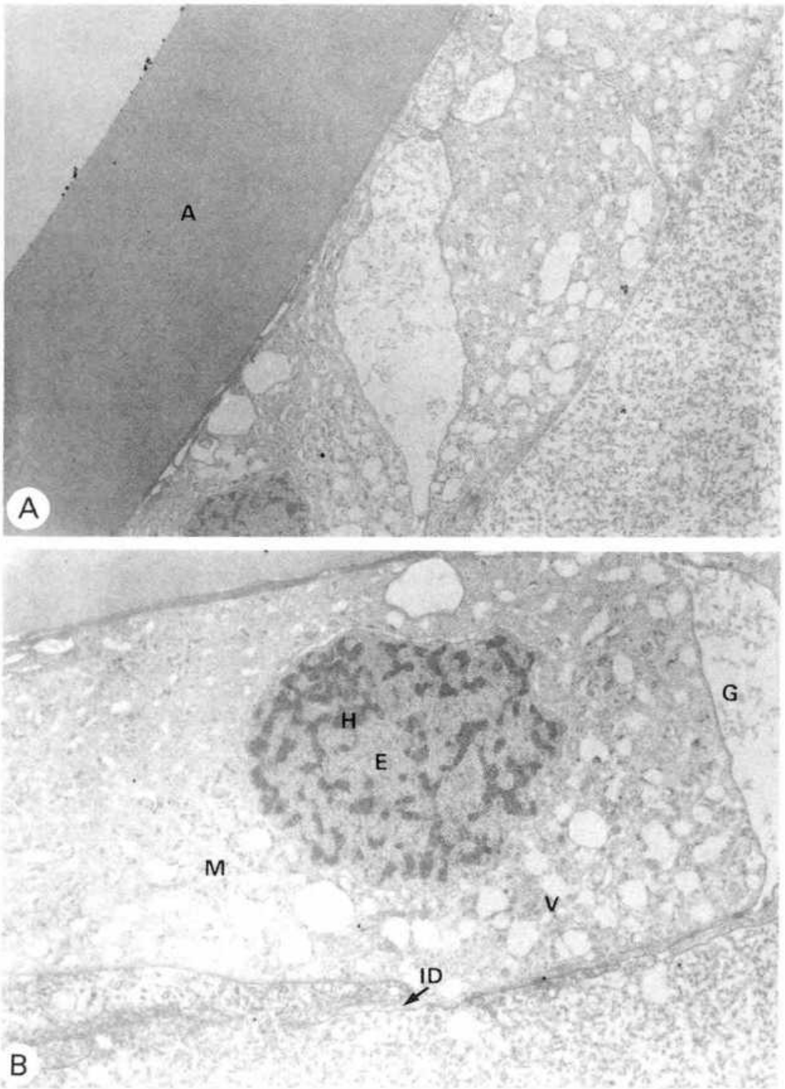


Figure 8 Electron microscopic findings of the anterior lens capsule. A: The anterior capsule (A) is homogeneous, and its anterior and posterior surfaces are smooth. (×2500.) B: Lens epithelial cell. The nucleus of the epithelial cell is round. The euchromatin (E) is finely granular. The heterochromatin (H) appears as aggregates. The cytoplasm contains small mitochondria (M) and many vacuoles (V). Adjacent cells have deep interdigitations (ID) and show many intercellular irregular gaps (G). (×4200.)

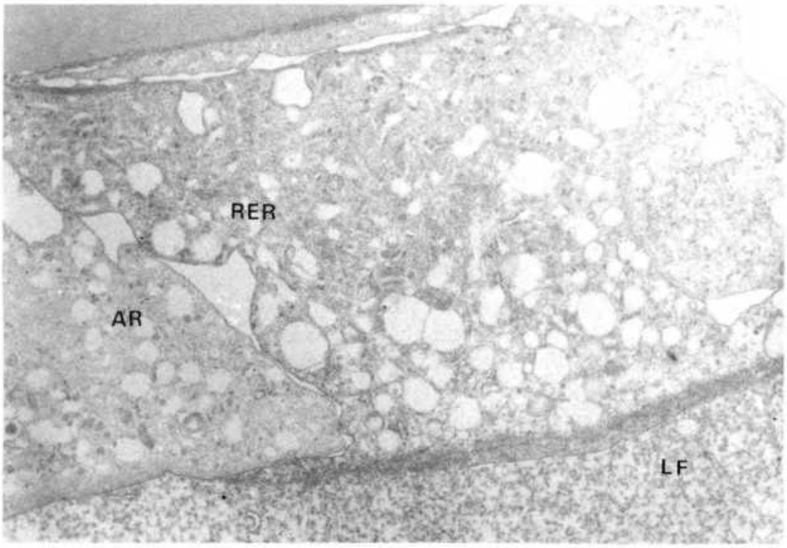


Figure 9 Lens epithelial cell and lens fibre. The cytoplasm contains rough surfaced endoplasmic reticulum (RER) and single or aggregated ribosomes (AR). The subepithelial lens fibres (LF) are degenerated and appear as evenly distributed granular masses. (×4200).

1 Weill G. Ectopie des crystallins et malformations générales. *Ann Oculist* 1932; **169**: 21–44.
2 Marchesani O. Brachydaktylie und angeborene Kugellinse als Systemerk-rankung. *Klin Monatsbl Angenheilkd* 1939: **103**: 392–406.
3 Jones RF. The syndrome of Marchesani. *Br J Ophthalmol* 1961; **45**: 377–81.
4 McGavic JS. Weill-Marchesani syndrome. *Am J Ophthalmol* 1966; **62**: 820–3.
5 Dodo T. The spherophakia-brachymorphia syndrome. *Nippon Ganka Gakkai Zasshi* 1857; **61**: 795–802.
6 Feiler-Obryv, Stein R, Godei V. Marchesani's syndrome and chamber angle anomalies. *Am J Ophthalmol* 1968; **65**: 862–6.
7 Ritch R, Wand M. Treatment of the Weile-Marchesani syndrome. *Ann Ophthalmol* 1981; **13**: 665–7.
8 Levy J, Anderson PE. Marchesani's syndrome. *Br J Ophthalmol* 1961; **45**: 223–6.
9 Willi M, Kut L, Cotlier E. Pupillary block glaucoma in the Marchesani syndrome. *Arch Ophthalmol* 1973; **90**: 504–8.
10 Ritch R, Podos SM. Argon laser treatment of angle-closure glaucoma. *Perspect Ophthalmol* 1980; **4**: 129–38.
11 Woodward PM. Anterior capsulotomy of dislocated lenses in Marchesani syndrome. *J Am Intraocul Implant Soc* 1984; **10**: 215–7.
12 Jensen AD, Cross HE. Ocular complications in the Weill-Marchesani syndrome. *Am J Ophthalmol* 1974; **77**: 261–9.
13 Wright KW, Chrousos GA. Weill-Marchesani syndrome with bilateral angle-closure glaucoma. *J Pediatr Ophthalmol Strabismus* 1985; **22**: 129–32.
14 Gorlin RJ, L'Heureux PR, Shapiro I. Weill-Marchesani syndrome in two generations: genetic heterogeneity of pseudodominance. *J Pediatr Ophthalmol* 1974; **11**: 139–44.
15 Young ID, Fielder AR, Casey TA. Weill-Marchesani syndrome in mother and son. *Clin Genet* 1986: **30**: 475–80.
16 Mullaney J. Normal development and developmental anomalies of the eye. In Garner A, Klintworth GK, eds. *Pathology of ocular disease*. New York: Dekker, 1982: 443–522.
17 Fujinaga Y, Matsunage H. *Cataract 40–47*. Tokyo: Kanehara Shuppan, 1987.
18 Klintworth GK, Garner A. The cause, types and morphology of cataracts. In: Garner A, Klintworth G, eds. *Pathology of ocular disease*. New York: Dekker, 1982: 1223–72.

British Journal of Ophthalmology, 1990, **74**, 635–637

Scleral melting in a patient with conjunctival rhinosporidiosis

R M L De Doncker, R J W de Keizer, J A Oosterhuis, A Maes

Abstract

A remarkable case of a scleral melting reaction in association with conjunctival rhinosporidiosis is presented and its surgical treatment with a scleral graft described.

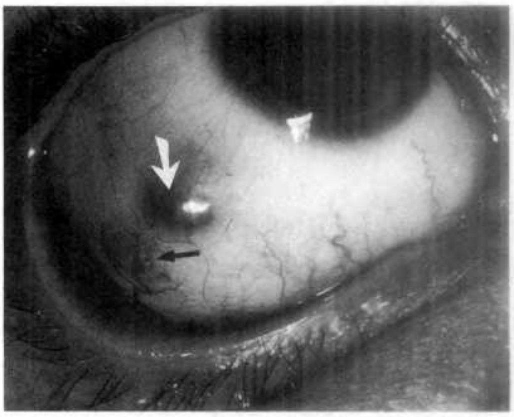


Figure 1 Scleral lesion (white arrow) and subepithelial conjunctival bodies (black arrow).

Rhinosporidiosis is a granulomatous disease of the mucous membranes, caused by *Rhinosporidium seeberi*, an organism of uncertain taxonomic position, most probably a fungus. It usually infects the mucous membranes of the nose and nasopharynx but may infect all other mucous membranes and even the skin.[1] Very rare cases of systemic infections of the liver and bones have been described.

The disease is worldwide but endemic in Africa and Asia, and most frequent in India and Sri Lanka. It occurs sporadically in other countries.[2-4] Inoculations of the eye and related structures are grouped as oculosporidiosis.[2] Most frequently the lacrimal sac is affected by extension from the nasal mucosa. Next most frequently the conjunctiva is subject to a primary infection, which may spread to the orbital tissue, the sclera, and the eyelids. A scleral defect associated with conjunctival rhinosporidiosis is rare, only two cases having been described. A third case is presented here.

Case report

A healthy 23-year-old white male agriculturist was referred to the ophthalmic outpatient department by his optician because he had noticed a bluish tumour on the temporal sclera of the right eye when fitting contact lenses. According to the patient this tumour had developed over one year and did not cause any trouble. There was no history of ocular disorder or trauma. The corrected visual acuity was 1·2 with +3·00 D.

Biomicroscopic examination of the cornea and the anterior chamber showed no abnormalities. In the inferior temporal part of the eye was a bluish circular swelling of the sclera about 4 mm in diameter. The overlying conjunctiva was movable over the scleral lesion. More temporal and under the margin of the scleral lesion were dilated conjunctival capillaries and scattered grey-white subepithelial corpuscular bodies of less than 1 mm diameter (Fig 1). The scleral lesion showed dim transillumination. It was decided to keep the lesion under observation.

Several months later the patient was examined because of an adenovirus keratoconjunctivitis. The scleral lesion had increased in size, and a strongly protruding scleral ectasia had developed, with considerable transillumination (Fig 2). Fundus examination at the site of the scleral lesion with the Goldmann contact lens revealed no retinal abnormalities. Diascleral B scan ultrasonography provided an acoustic-free scleral image at that site without signs of chorioretinal lesions. On fluorescein angiography no abnormal conjunctival or scleral vessels were seen; the scleral lesion was delineated by hypofluorescence (Fig 3). The results of these investigations pointed to a scleral defect.

Because of impending perforation of the globe it was decided to perform a homograft of preserved human sclera over the scleral staphyloma. First an argon-laser coagulation of the retina round the lesion was performed. To obtain maximal reduction of the intraocular pressure during surgery mannitol was administered intravenously, and paracentesis and a large canthotomy were performed. The abnormal part of the conjunctiva was resected; Tenon's capsule was kept intact. A 10 mm diameter scleral homograft was inserted over the 8 mm diameter defect with interrupted 6-0 silk sutures (Fig 4). In addition a running suture of 10-0 silk was placed over the margin of the graft (Fig 5). During a two-year follow-up the conjunctival

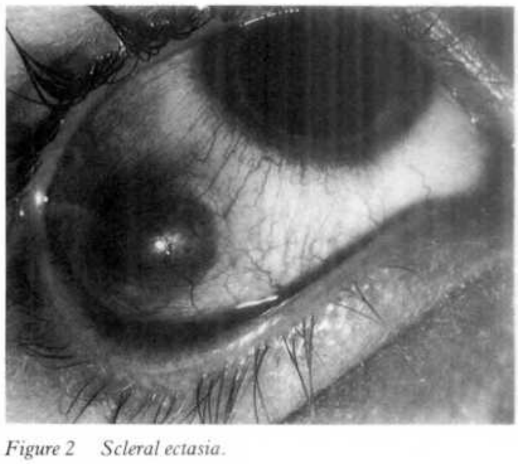


Figure 2 Scleral ectasia.

Department of Ophthalmology, University Hospital, Leiden, The Netherlands
R M L De Doncker
R J W de Keizer
J A Oosterhuis

Department of Pathology, University of Leiden, Leiden, The Netherlands
A Maes

Correspondence to:
R M L De Doncker,
Department of Ophthalmology, University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands.

Accepted for publication
26 April 1990

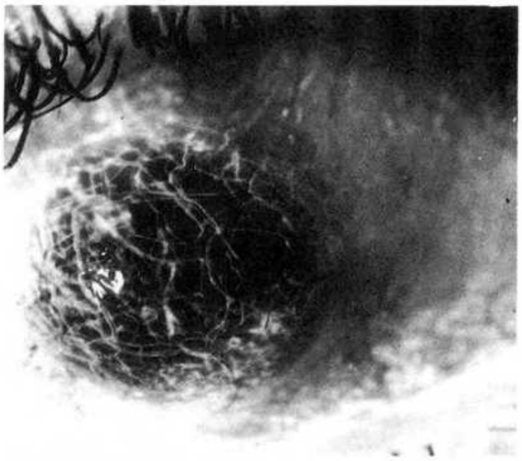


Figure 3 Anterior segment fluorescein angiography of the scleral lesion.

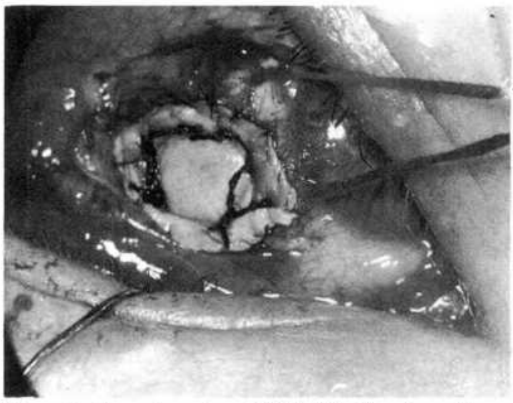


Figure 5 A running suture of 10-0 silk is placed over the margin of the homograft.

infection showed no relapse, nor were there signs of graft failure.

HISTOPATHOLOGY

Light and electron microscopic examination of the conjunctival lesions showed a typical appearance. Below a normal epithelium many double walled cysts were observed in the conjunctival stroma, with an inner layer staining strongly positive with periodic acid Schiff and an outer Alcian blue positive layer. The cysts contained many vacuoles and eosinophilic granular material (Figs 6, 7, 8). These cysts were typical of rhinosporidium spores in different stages of maturity.

Discussion

Conjunctival rhinosporidiosis is a well known ocular infection. Clinically it causes vascularised, dark red, polypoid masses.[5,6] The surface of the polyps is covered with distinct grey-white spherules (sporangia). The granulomatous masses can grow to resemble mucosal tumours.[7]

The ratio of nose to eye infections is 4·6/1.[8] In contrast to conjunctival sporotrichosis and coccidioidomycosis Parinaud's oculoglandular syndrome never occurs. The mode of infection is unknown; experimental inoculation in animals has been unsuccessful, and cultures of the organism have failed to grow.[9]

Transmission from animals to humans has never been seen. It is mainly children and young male adults who are affected. In all studies[6,10,11] a male-female ratio of 4·3/1 is found. Epidemiological studies showed that conjunctival rhinosporidiosis has a predilection for agricultural workers,[10] so that contact with contaminated soil may be a causative factor. Light and electronmicroscopic studies[12-14] have provided most information on the organism. A young trophocyte undergoes nuclear division until it contains over 4000 nuclei. The inner layer of the trophocyte membrane differentiates, and a mature sporangium containing thousands of endospores is formed. The free spores can be isolated in the tears of an affected person.

Scleral melting in association with conjunctival rhinosporidiosis is very rare, having until now been described only twice.[6,15] In contrast to the normal clinical picture the granulomatous reaction of the conjunctiva in our patient was less obvious; a scleral defect with scattered grey-white subepithelial granules on the margin was the main symptom.

The clinical diagnosis of this type of scleromalacia is based on the concomitant conjunctival findings, but light and electronmicroscopic examinations were required for the confirmation of the diagnosis. A differential diagnosis from other non-inflammatory scleral melting syndromes must be made (Table 1). Scleromalacia perforans is more frequent than rhinosporidiosis and affects the eyes of persons with seropositive rheumatoid arthritis. Spontaneous intercalary perforation is unrelated to rheumatoid arthritis and affects persons of a younger age.

The only effective treatment is radical surgical excision followed by thermal and chemical coagulation. Nevertheless, relapse is the rule rather than the exception.

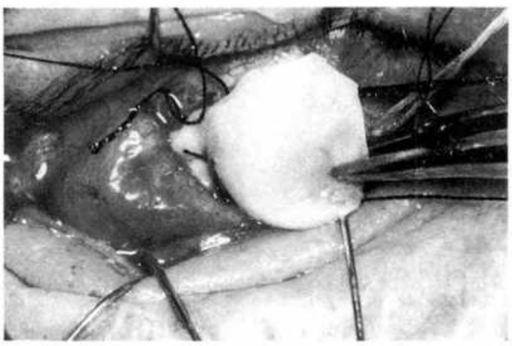


Figure 4 Preserved sclera is placed over the scleral ectasia by interrupted sutures of 6-0 silk.

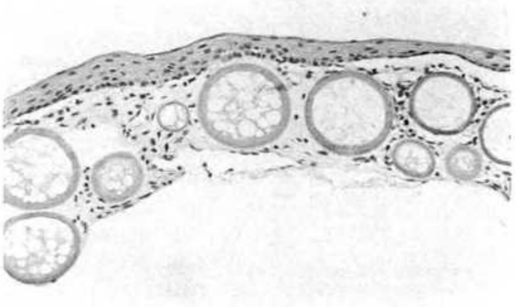


Figure 6 Light microscopic section of preserved conjunctival lesion. In the lamina propria numerous cysts are seen. (Haematoxylin-eosin, ×30.)

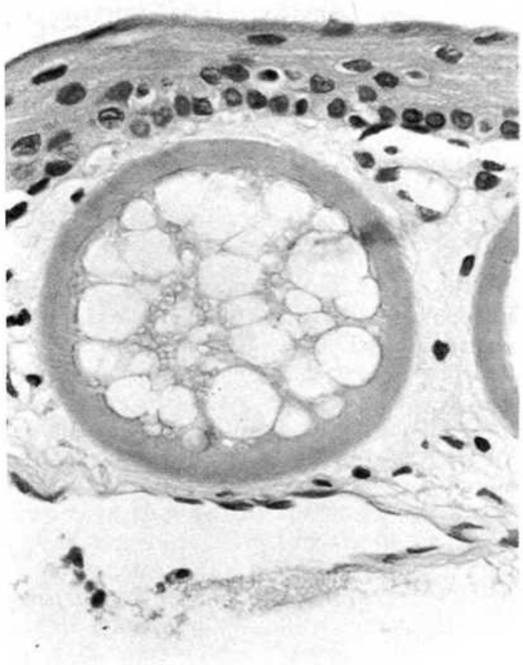


Figure 7 One cyst in detail contains granular eosinophilic material and lipid vacuoles. (Haematoxylin-eosin, ×53.)

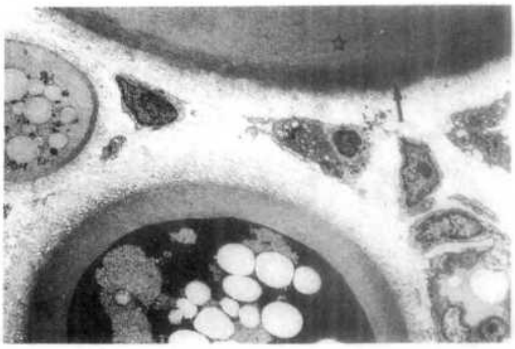


Figure 8 Electron micrograph of a young trophocyte (sporoblast) showing the homogeneous electron-dense DNA material and the lipid bodies. At the top of the image the bilaminar wall of a trophocyte in a later stage of endosporulation is seen. Notice the inner homogeneous electron-dense layer (open asterix) and the outer granular layer (arrow). (×2625.)

*Table 1 A differential diagnosis between the various conditions with scleral melting**

	Scleromalacia perforans	*Spontaneous intercalary perforation*	*Hyaline plaques*	*Rhinosporidiosis scleral melting, 3 cases*
Age	50–75	25–50	60–75	<25
Sex	Females	Either	Either	Males
Rheumatoid arthritis	Constant	Unrelated	Unrelated	Unrelated
Binocularity	Bilateral	Either	Bilateral	Either
Distribution	Multiple	Single	Symmetrical	Single
Inflammation	Nil	Nil	Nil	Nil
Pathology	Necrosis	Unknown (atrophy?)	Degeneration	Unknown (immunological or enzymatic?)
Pain	Nil	Nil	Nil	Nil
Evolution	Progressive	Stationary	Stationary	Progressive
Prognosis	Bad	Good	Good	Bad

*Partly reprinted from Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1965; **8:** 1055.

No medical treatment has proved to be effective in the systemic and mutilating conditions. Griseofulvin and amphotericin have been used without success. In cases of scleral ectasia a homograft of preserved human sclera gives good results.

The pathological basis of the scleral melting reaction in the immediate environs of the conjunctival infection is obscure. The absence of direct contact between conjunctival lesions and the scleral defect suggests that an immunological or enzymatic process could be the cause. Further investigation has so far been impossible because attempts to culture the spore have been without success.

1 Desai SC. Ein Überblick über die Rhinosporidiose. *Mykosen* 1961; **4:** 64–8.
2 François J, Rysselaere M. *Oculomycoses*. Springfield: Thomas, 1971: 361–9.
3 Neumayr TG. Bilateral rhinosporidiosis of the conjunctiva. *Arch Ophthalmol* 1964; **71:** 379–81.
4 Jimenez JF, Young DE, Hough AJ. Rhinosporidiosis. A report of two cases from Arkansas. *Am J Clin Pathol* 1984; **82:** 611–5.
5 Satyendran OM, Jagannadha Row, Phatak BK, Sarma SR. Rhinosporidiosis of the eye and adnexa. *Orient Arch Ophthalmol* 1965; **3:** 332–5.
6 Kuriakose ET. Oculosporidiosis. Rhinosporidiosis of the eye. *Br J Ophthalmol* 1963; **47:** 346–9.
7 Sharma KD, Shrivastav JB, Agarwal S. Ocular rhinosporidiosis simulating a tumour. *Br J Ophthalmol* 1958; **42:** 572–4.
8 Karunaratne WAE. *Rhinosporidiosis in man*. London: Athlone Press, University of London, 1964.
9 Grover S. *Rhinosporidium seeberi*: a preliminary study of the morphology and life cycle. *Sabouraudia* 1970; **7:** 249–51.
10 Owor R, Wamukota WM. Rhinosporidiosis in Uganda. A review of 51 cases. *East Afr Med J* 1978; **55:** 582–6.
11 Kannan Kutty M, Sreedharan T, Mathew KT. Some observations on rhinosporidiosis. *Am J Med Sci* 1963; **246:** 695–701.
12 Defrenne P, Dorzee J, Appelmans M, Jansen E. Conjunctivite proliférante par *'Rhinosporidium seeberi'*. *Bull Soc Belge Ophthalmol* 1953; **104:** 247–52.
13 Sood NN, Narayana S. Rhinosporidium granuloma of the conjunctiva. *J Pediatr Ophthalmol Strabismus* 1969; **6:** 141–4.
14 Savino DF, Margo CE. Conjunctival rhinosporidiosis. Light and electron microscopic study. *Ophthalmology* 1983; **90:** 1482–9.
15 Lamba PA, Shukla KN, Ganapathy M. Rhinosporidium granuloma of the conjunctiva with scleral ectasia. *Br J Ophthalmol* 1970; **54:** 565–8.

British Journal of Ophthalmology, 1990, 74, 638

Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy

A Hirsh, A Alhalel, A Weiss, H Brener, I Avni

Abstract

Bilateral total corneal epithelial erosion and descement folds are reported as toxic side effects of 5-fluorouracil in a patient with end stage carcinoma of the stomach.

The antimetabolite 5-fluorouracil (5-FU) is a pyramidine analogue that has shown significant activity against carcinomas of the breast and gastrointestinal and genitourinary tracts. The drug is generally administered by rapid intravenous injection and has a plasma half time of 10 minutes. The most noted side effects of parenteral 5-FU include nausea, vomiting, stomatitis, dermatitis, alopecia, and peripheral neuropathy.[1-3] Cerebellar ataxia may be seen after three to four weeks due to accumulation of fluorocitrate, which is a metabolic product of 5-FU and known as a potent inhibitor of the Krebs cycle in cerebellar tissue.[4]

The main known eye disorders among the toxic side effects of 5-FU are epiphora, hyperaemia, blepharitis, conjunctivitis, and blurred vision. These have usually resolved rapidly after the drug is discontinued.[4-6] A direct correlation between the amount of lacrimation and the concentration of the drug in the tears has been found.[7] The systemic use of the drug can cause tear duct fibrosis.[8] Cicatricial ectropion has also been described in patients with excessive lacrimation receiving 5-FU.[9] Oculomotor disturbances, especially weakness of convergence or divergence due to regional 5-FU neurotoxicity affecting the brain stem, have been described.[10] In the following report we present a rare case of bilateral total corneal epithelial erosion and descement folds in a patient treated with intravenous 5-FU as a palliative for carcinoma of the stomach.

Case report

A 67-year-old man was referred to the Eye Department from the Oncology Clinic of our hospital because of sudden decreased visual acuity. Seven days after admission he was treated with a chemotherapeutic course of 170 mg 5-FU daily for carcinoma of the stomach. This treatment was discontinued on the fourth day because of the appearance of nausea, vomiting, and stomatitis, together with blurred vision on the second day.

On examination the visual acuity was 6/60 in both eyes, and the intraocular pressure was normal. No signs of epithora or conjunctival irritation were present. Both corneas showed total epithelial erosion and descement folds. The anterior chambers were deep, with no reaction. The retina and the optic nerve were normal.

The patient was treated with synthomycin ointment 5% and patches, and was examined the following day, with identical findings. Unfortunately he died a day later from cardiorespiratory arrest.

Since the metabolism of the cornea is mainly from the aqueous humour and the tear film,[11] a drug affecting the corneal epithelium and stroma after systemic administration is expected to achieve toxic levels in both fluids. The appearance of conjunctivitis following systemic 5-FU therapy has been reported before, and it is related to the toxic side effects on all mucous membranes. In our case the corneal involvement appeared two days after a severe stomatitis.

In conclusion, corneal epithelial erosion and descement folds may represent a potential toxic side effect of 5-FU, and may appear as a part of its clinical manifestations.

Chaim Sheba Medical Center, Tel-Aviv University, Sackler School of Medicine, Israel
Goldschleger Eye Institute
A Hirsh
A Alhalel
I Avni

Department of Oncology
A Weiss
H Brener

Correspondence to:
A Hirsh, MD, Chaim Sheba Medical Center, Tel-Aviv University, Sackler School of Medicine, Israel

Accepted for publication
11 April 1990

1 Ansfield FJ, Schnoeder JM, Cursen AF. Five years clinical experience with 5-FU *JAMA* 1962, 181: 295–9
2 Mortel CG Chemotherapy of gastrointestinal carcinoma. *Clin Gastroenterol* 1976; 5: 777–93.
3 Chabner BA, Myer CE. Clinical pharmacology of cancer chemotherapy In: DeVita VT, Hellman S, Rosenberg SA, eds *Cancer Principles and practice of oncology*. Philadelphia. Lippincott, 1989 349–95
4 Griffin DJ, Garnick MB. Eye toxicity of cancer chemotherapy a review of the literature. *Cancer* 1981, 48: 1539–49
5 Fraunfelder FT. Interim report: national registry of possible drug-induced ocular side effects *Ophthalmology* 1980, 87: 87–90
6 Fraunfelder FT, Meyer SM Ocular toxicity of antineoplastic agents *Ophthalmology* 1983, 90: 1–3
7 Hamersley J, Luce JK, Florentz TF, Burkholder MM, Pepper JJ. Excessive lacrimation from fluorouracil treatment *JAMA* 1973; 225: 747–8
8 Haidak DJ, Hurwitz BS, Yeung KY. Tear duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Am Intern Med* 1978; 88: 657
9 Straus DJ, Mansolf FA, Ellerby RA, McCracken JD Cicatricial ectropion secondary to 5-fluorouracil therapy *Med Pediatr Oncol* 1977; 3. 9–15
10 Brixenman WW, Nicholls JVV, Warwick OH Oculomotor disturbances associated with 5-FU chemotherapy. *Am J Ophthalmol* 1977; 88: 789–93
11 Woltman SR, Hart WM In: Moses RA, Hart MH, eds *Adler's physiology of the eye clinical application* St Louis: Mosby, 1987: 45–7

LETTERS TO THE EDITOR

Local anaesthesia without retrobulbar injection

SIR,—I refer to the two papers on local anaesthesia without retrobulbar injection.[1,2] I have been using a similar technique since 1985 and have presented a paper entitled 'Alternative to retrobulbar anaesthesia' at the 1986 Malaysia–Singapore Ophthalmic Conference, and recently another paper entitled 'Transconjunctival peribulbar anaesthesia – 1200 cases' at the XXVI International Congress of Ophthalmology held in Singapore in March 1990.

I agree that the transconjunctival method is safer than the percutaneous methods of local anaesthesia (retrobulbar or peribulbar). As you had pointed out in the papers referred to, the analgesia achieved by local infiltration is just as good, if not better than, with retrobulbar injection. It is certainly better than that achieved with the percutaneous peribulbar techniques that require about 10 ml of anaesthetic. However, the akinesia achieved is not so good. This is not a problem, as residual movement is in the horizontal plane and not very extensive.

The other problem, which is not mentioned in these papers, is the chemosis caused by the subconjunctival injection. It makes insertion of the superior rectus bridle suture and the corneoscleral or limbal section difficult. These problems can be overcome by inserting the superior rectus suture first, before the subconjunctival injection. This is painless if amethocaine eyedrops have been instilled beforehand. The superior rectus suture is then used to draw the globe downwards for proper placement of the anaesthetic injection, which, as is stated in the papers, should be 7 mm behind the limbus. If the superior rectus suture is not used to draw the globe downwards, the tendency is to place the injection too anteriorly with cumbersome chemosis to deal with. (Some patients do not look downwards far enough, particularly Asian patients, who have small palpebral fissures).

Injecting some local anaesthetic (0·5 ml) into the lower fornix improves akinesia and allows for the painless injection of drugs, such as antibiotics and steroids, postoperatively.

I have stopped using retrobulbar anaesthesia for the past five years, and it is a wonderfully rewarding feeling to know that the patient I am injecting will not have retrobulbar haemorrhage or worse complications associated with retrobulbar injections.

C Y KHOO
Mount Elizabeth Medical Centre,
Singapore 0922

1 Redmond RM, Dallas NL. Extracapsular cataract extraction under local anaesthesia without retrobulbar injection. *Br J Ophthalmol* 1990; **74:** 203–4.

2 Smith R. Cataract extraction without retrobulbar anaesthetic injection. *Br J Ophthalmol* 1990; **74:** 205–7.

SIR,—I read Dr Khoo's letter with great interest and agree with many of his comments. He does not mention whether hyaluronidase is a component of the anesthetic solution that he uses. Without this, bulky conjunctival swelling can be a hindrance.

Furata *et al.*[1] have recently published their experience of subconjunctival anaesthesia in cataract surgery. It is apparent that there is a proliferation of different terms to describe essentially the same technique: subconjunctival, subtenon's, peribulbar, transconjunctival peribulbar, limbal, etc. I favour the first term, as techniques such as subconjunctival injection of antibiotic are analogous. In my view, the most essential aspect of this technique is to establish adequate *lid* paralysis before opening the eye.

R M REDMOND
Eye Clinic,
Royal Victoria Hospital,
Grosvenor Road,
Belfast,
Northern Ireland

1 Furuta M, Toriumi T, Kashiwagi K, Satoh S. Limbal anestheisa for cataract surgery. *Ophthalmic Surg* 1990; **21:** 22–5.

⁂ I also read Dr Khoo's letter with interest. It is true that the injection chemosis sometimes interferes with the superior rectus suture, but usually not. Occasionally I have had to open the conjunctiva first – and identify the rectus tendon direct. I have not tried putting in the suture first as I believed this would be too painful. – ED., *BJO*.

Local anaesthesia for cataract surgery

SIR,—In response to Mr Steele's editorial (*BJO* April, 1990, p 195) regarding anaesthetic techniques for cataract surgery, 566 day care ophthalmic operations were performed at this hospital between February 1987 and December 1989, the majority being cataract extractions with lens implantation in elderly patients. 31% (176) were performed under general anaesthesia. Complications of general anaesthesia were one chest infection and one episode of urinary retention. The latter patient was readmitted on the afternoon of surgery and subsequently underwent resection of a malignant prostate. Complications of local anaesthesia included four retrobulbar haemorrhages and one intrathecal/intra-arterial injection of bupivacaine 0·5%.

We have recently completed a randomised prospective study of cognitive function in elderly patients undergoing cataract extraction under local or general anaesthesia. At one and three months after surgery there was no difference between the local and general anaesthesia groups.

It would appear that modern general anaesthetic techniques are such that patients, ophthalmic surgeons, and anaesthetists may safely choose any combination of inpatient or outpatient surgery under general or local anaesthesia.

M G KERR-MUIR
G O'SULLIVAN
St Thomas's Hospital,
London SE1 7EH

Trial frame for children

SIR,—It is not easy to find a comfortable trial frame for children under the age of 5. The commercial ones available are usually too big. The head band design is often frightening to a child. Similarly, loose lenses or a retinoscopy rack are unsuitable for the objective assessment of astigmatism.

I have found the use of NHS frame C525 with plain plastic lenses and Halberg clips useful (Fig 1). A comparable current frame is Merx PS80. It is fairly easy to align the 90° axis vertically, though inadvertent rotation is of course possible. There are two cells available for spherical and/or cylindrical lenses.

MICHAEL D O'RIORDAN
Croydon Eye Unit,
33 Mayday Road,
Thornton Heath,
Surrey CR4 7XN

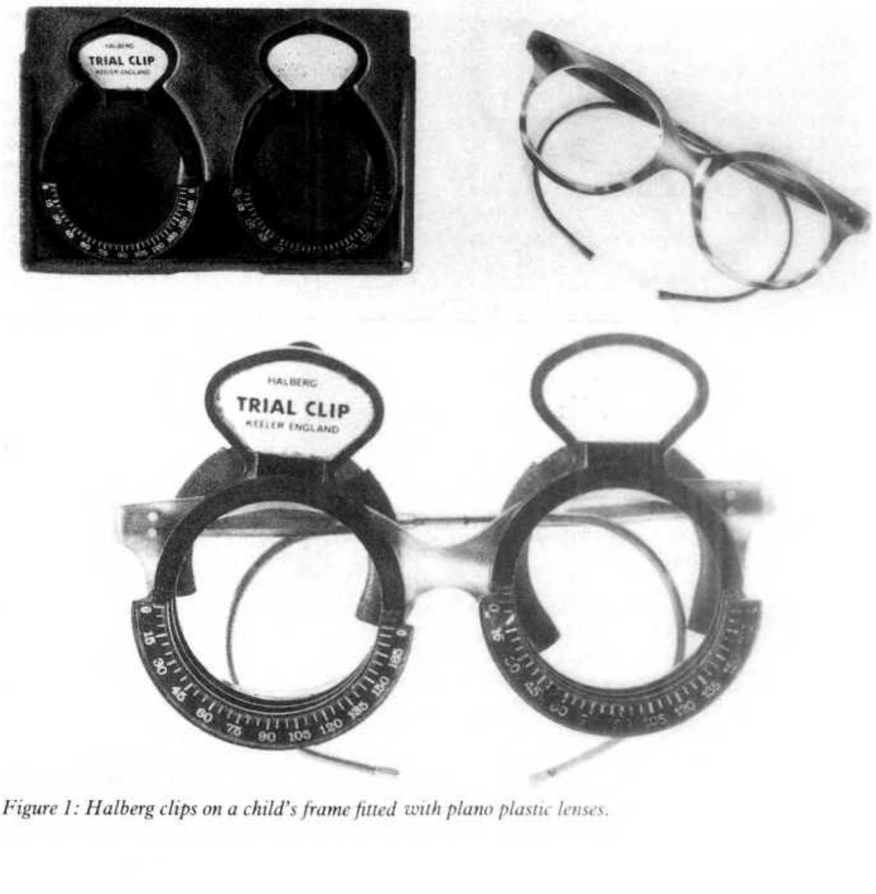


Figure 1: Halberg clips on a child's frame fitted with plano plastic lenses.

Adult pure red cell aplasia following topical ocular chloramphenicol

SIR,—Pure red cell aplasia is a disorder characterised by a hyporegenerative anaemia due to a bone marrow failure involving erythropoiesis alone.[1] This disorder has been observed following the administration of a variety of drugs [2] We report a case of pure red-cell aplasia after topical ocular administration of chloramphenicol, a drug which has rarely been associated with this disorder.[2,3]

An 85-year-old man was admitted to hospital because of fatigue and progressive dyspnoea. There was no significant past medical history and he had not taken any drugs The only known exposure to drugs or chemicals was the use of chloramphenicol eyedrops for the previous two months Clinical examination revealed paleness of the skin and mucosae Chest roentgenogram, electrocardiogram, and the appearances on oesophageal and gastric endoscopy were normal The laboratory results showed an erythrocyte sedimentation rate of 90 mm in one hour, erythrocytes $1{\cdot}35\times10^{12}$/l, haemoglobin 51 g/l, mean corpuscular volume 108 fl, leucocytes $3{\cdot}8\times10^{9}$/l (30% neutrophils, 50% lymphocytes, 14% monocytes, 5% eosinophils, and 1% basophils), platelets 227×10^{9}/l and reticulocytes 2×10^{9}/l. Viral serological tests were negative, and the results of an immunological battery of tests, lymphocyte subpopulations, and thyroid hormone serum levels were normal. The serum iron level was 30·98 μmol/l, transferrin 15·9 μmol/l, ferritin 5580 ng/ml, saturation index 83·6%, and serum levels of folic acid, vitamin B_{12}, and haptoglobin were within normal limits. A bone marrow aspirate and biopsy showed pure red cell aplasia (1%), normal myeloid and megakaryocytic precursors, reactive eosinophilia, and plasmocytosis. The red cell aplasia persisted despite withdrawal of chloramphenicol and treatment with 6-methylprednisolone, and the patient still has to be transfused periodically with red blood cell concentrates two years after diagnosis. A second bone marrow examination performed six months later revealed no changes from the previous one.

The major adverse reaction following chloramphenicol is bone marrow depression, usually manifested as pancytopenia but occasionally as isolated thrombocytopenia, leucopenia, or erythroblastopenia.[3] This drug has been shown to cause two distinct types of bone marrow toxicity: a 'dose-related' and usually reversible depression, and a much more severe 'idiosyncratic' type of reaction.[4] The majority of adverse reactions have been associated with the oral administration of the drug, but other routes such as the intravenous, cutaneous, and ocular have also been reported.[3,5] Although several cases after ocular exposure have been published,[5] there is some controversy about the relation between this route of administration and chloramphenicol toxicity. The mechanism seems to be the idiosyncratic type, and most cases have occurred within four months of the initial exposure to the drug.[6]

Our patient developed pure red cell aplasia after using chloramphenicol eyedrops for two months. The depression of the bone marrow did not recover following withdrawal of the drug

In view of the potential risks the administration of chloramphenicol eyedrops should be restricted to absolutely specific indications.

TOMAS FERNANDEZ DE SEVILLA
JOSE ALEGRE
TERESA VALLESPI
VICENTE FALCO
JOSE MANUEL MARTINEZ-VAZQUEZ
Department of Internal Medicine,
Department of Haematology,
Hospital General Vall d'Hebrón',
08035 Barcelona, Spain

1 Krantz SB Pure red-cell aplasia *N Engl J Med* 1974, 291· 345–50
2 Geary CG Red cell aplasia In: C G Geary, ed *Aplastic anaemia* London· Baillière Tindall, 1979. 195–229
3 Chaplin S Bone marrow depression due to mianserin, phenylbutazone, oxyphenbutazone, and chloramphenicol Part II. *Adverse Drug React Acute Poisoning Rev* 1986, 3: 181–96
4 Yunis AA Chloramphenicol induced bone marrow suppression *Semin Hematol* 1973; 10. 225–34
5 Besamusca FW; Bastiaensen LA Blood dyscrasias and topically applied chloramphenicol in ophthalmology *Doc Ophthalmol* 1986, 64. 87–95.
6 Fraunfelder FT, Meyer SM. Systemic reactions to ophthalmic drug preparations *Med Toxicol Adverse Drug Exp* 1987; 2: 287–93

NOTES

Paediatric surgery

The Fourth Paediatric Surgery Workshop will be held on 7-8 June 1991 at the Japanese-German Centre, Berlin. Further information from: Dr F Schier, Universitatsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany.

Hong Kong meetings

The Hong Kong Ophthalmological Society will hold a clinical meeting in association with the 5th Clinical Ophthalmological Symposium on 1-2 December 1990. The theme of the society's meeting will be 'Eye disorders of childhood.' Further details from The Secretariat, Scientific Meeting 1990, Hong Kong Ophthalmological Society, c/o Hong Kong Medical Association, 5/F Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong.

Ophthalmic photography

The British Ophthalmic Photographic Association's 6th Annual Conference will be held in Edinburgh on 16-17 November 1990. The Kodak lecturer this year is Professor David McLeod Further details from: Mrs Angela Ellingford, Senior Ophthalmic Photographer, Polyclinic 6a, Ninewells Hospital, Dundee, Scotland Tel 0382-60111, ext 3219)

Symposium on vision

A satellite symposium of the Asian and Oceanian Physiological Societies (AOPS) on 'Vision, with emphasis on electrophysiology' will be held at the Malabar Hotel, Willingdon Island, Cochin, India, on 4 November 1990 Details from Dr JK Mukkadan, Little Flower Medical Research Centre, PO Box 23, Angamally-683 572, Kerala, South India.

International symposium

The German Ophthalmological Society will sponsor an International Symposium in Bonn-Köln on 19 to 21 September 1991 The symposium will cover both clinical and research aspects of ocular infections and will include a basic sciences course. Call for papers is open. Further details from: Alexander A Bialasiewicz, MD, University Eye Hospital Bonn, Sigmund Freud Str. 25, 53 Bonn 1, West Germany

---

FIFTY YEARS AGO

The National Register of Medical Auxiliary Services. Orthoptists. British Medical Association, London. 1940

A review of the second edition of the National Register of Medical Auxiliary Services appeared in our columns last year, p 357 In it we expressed the hope that future editions would include the names of those undertaking orthoptic training. The Board of Registration of medical Auxiliaries has lately recognised the British Orthoptic Society as a qualifying body in orthoptics, and members of the Society have been enrolled in the National Register This Orthoptic Supplement to the Register is the result, and will be most welcome to all ophthalmic surgeons The number of registered orthoptists is not large and all the more is it essential for surgeons to be able to get the names and addresses of those who are qualified and registered.

Copies of the supplement can be obtained by application to the Registrar, Board of Registration of Medical Auxiliaries, British Medical Association House; Tavistock Square, London WC1

Br J Ophthalmol 1940, **24:** 197

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors** **Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- **24 hour delivery.**
- **Courier services.**
- **Personal delivery.**

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia
Advancing The New Biology

NEW FORMULATION
When
nature runs dry . . .
HYPOTONIC
LIQUIFILM®
polyvinyl alcohol
TEARS
NEW HYPOTONIC FORMULATION
to help restore normal tearfilm tonicity
in lipid, aqueous and mucin deficient eyes[1]
FOR SUCCESS FROM THE START – FIRST TIME

CENTRAL LIBRARY

Liquifilm Tears Prescribing Information
Presentation: Clear, colourless to slightly straw-coloured, sterile, aqueous ophthalmic solution containing Liquifilm (polyvinyl alcohol) USP 1.4% (w/v). Also contains disodium edetate Ph Eur 0.015% (w/v), benzalkonium chloride Ph Eur 0.005% (w/v) with sodium chloride Ph Eur, sodium phosphate Ph Eur and purified water Ph Eur. **Uses:** Liquifilm Tears is an ocular lubricant for the relief of dry eye and dry eye symptoms. **Dosage and administration:** For all ages. One or two drops administered topically to the affected eye(s) as required. **Contra-indications, warnings etc:** *Contra-indications:* Sensitivity to any of the components. Not for use with soft (hydrophilic) contact lenses because of the presence of benzalkonium chloride as a preservative. *Warnings:* If irritation increases or persists, discontinue use. **Pharmaceutical precautions:** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category:** P. **Package quantities:** LIQUIFILM TEARS is available in plastic dropper bottles containing 15 ml. **Basic NHS Cost:** (as at November 1988) £1.33. **Further Information:** Nil. **Product Licence Number:** PL 0426/0009R. **Date of preparation:** July 1988. **Reference:** 1. Bron AJ. Trans Ophthalmol Soc U.K. (1985); **104:** 801-826.

ALLERGAN PHARMACEUTICALS™
SCIENCE WITH VISION

Full prescribing information is available on request.
Allergan Limited, High Wycombe, Bucks. HP12 3SH. ®denotes registered trade mark

22. 4. 91

VCM

NOVEMBER 1990 VOL 74 NO 11

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial
641 Fluorosilicone oil for retinal detachment *J D Scott*

Original articles
643 Fluorosilicone oil in the treatment of retinal detachment *Charles M Gremillion Jr, Gholam A Peyman, Kwan-Rong Liu, Khaled S Naguib*

647 Intraocular pressure changes and postural changes of intraocular pressure in experimentally induced Hansen's disease of rhesus, mangabey, and African green monkeys *Naushad Hussein, Bruce Ostler, Bobby J Gormus, Robert Wolf, Gerald P Walsh*

650 A survey of the initial referral of children to an ophthalmology department *Wang Yu-dong, J R Thompson, D B Goulstine, A R Rosenthal*

654 Biometry of the crystalline lens in early-onset diabetes *John M Sparrow, Anthony J Bron, Nicholas A Phelps Brown, H A W Neil*

661 Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract *Nurettin Akyol, Orhan Değer, E Edip Keha, Saim Kiliç*

663 Topical timolol and serum lipoproteins *James West, Simon Longstaff*

665 Haemorheological changes in patients with retinal vein occlusion after isovolaemic haemodilution *J Wiek, M Schade, M Wiederholt, H R Arntz, L L Hansen*

670 Cytopathology of adenovirus keratitis by replica technique *Prabhat C Maudgal*

676 Pupillary responses in amblyopia *Alison Y Firth*

681 The electroretinogram in minimal diabetic retinopathy *T C A Jenkins, J P Cartwright*

Mini review
685 Supply of corneal tissue in the United Kingdom *W J Armitage, S J Moss, D L Easty, B A Bradley*

Case reports
688 Multifocal posterior uveitis: clinical and pathological findings *David G Charteris, William R Lee*

694 Linear scleroderma associated with ptosis and motility disorders *Maria S A Suttorp-Schulten, Leo Koornneef*

696 Homocystinuria presenting as central retinal artery occlusion and longstanding thromboembolic disease *W v d Berg, F D Verbraak, P J M Bos*

698 Chickenpox chorioretinitis *S P Kelly, A R Rosenthal*

700 Choroidal osteoma (osseous choristoma): an atypical case *G Cennamo, G Iaccarino, G de Crecchio, G Liguori*

702 Lobular pattern of choriocapillaris in pre-eclampsia with aldosteronism *Yoshihiro Saito, Tatsuya Omoto, Masakatsu Fukuda*

704 **Letters to the editor Fifty years ago**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE

Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Journal

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced*.

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof, and should read it carefully for printers' errors. Alterations to the original text should be kept to a minimum and may be charged to the author.

REPRINTS may be ordered from the Publishing Manager when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Ophthalmology*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not, however, required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents of the publication without prior permission is always illegal.

NOTICE TO ADVERTISERS Applications for advertisement space and for rates should be addressed to the Advertisement Manager, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *British Journal of Ophthalmology* is published monthly. The annual subscription rates are £106.00 inland and £126.00 overseas (US $200.00). Orders should be sent to the Subscription Manager, British Journal of Ophthalmology, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. All inquiries regarding air mail rates and single copies already published should be addressed to the Publisher in London.

Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd

OH DEAR,
I FORGOT TO TAKE ALL MY DROPS
AGAIN.

What can you give a patient who suffers from amnesia as well as glaucoma?

Getting patients to comply with complicated ose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, e beta blocker most patients only need to take nce a day. This is possible because of Betagan's stained activity over 24 hours,[1] hich has been shown to be ffective in controlling the traocular pressure of up to 1% of patients on a once aily dose.[2]

In fact, in a study evaluating once-daily Betagan the authors concluded "once-daily treatment with levobunolol appeared to be as effective as twice-daily treatment while offering greater convenience and comfort and potentially greater safety."[3] So next time you're looking for a simple but flexible treatment for open angle glaucoma, consider Betagan.

It's a name worth remembering.

NEW

BETAGAN®

(levobunolol hydrochloride 0.5%)

ONCE DAILY

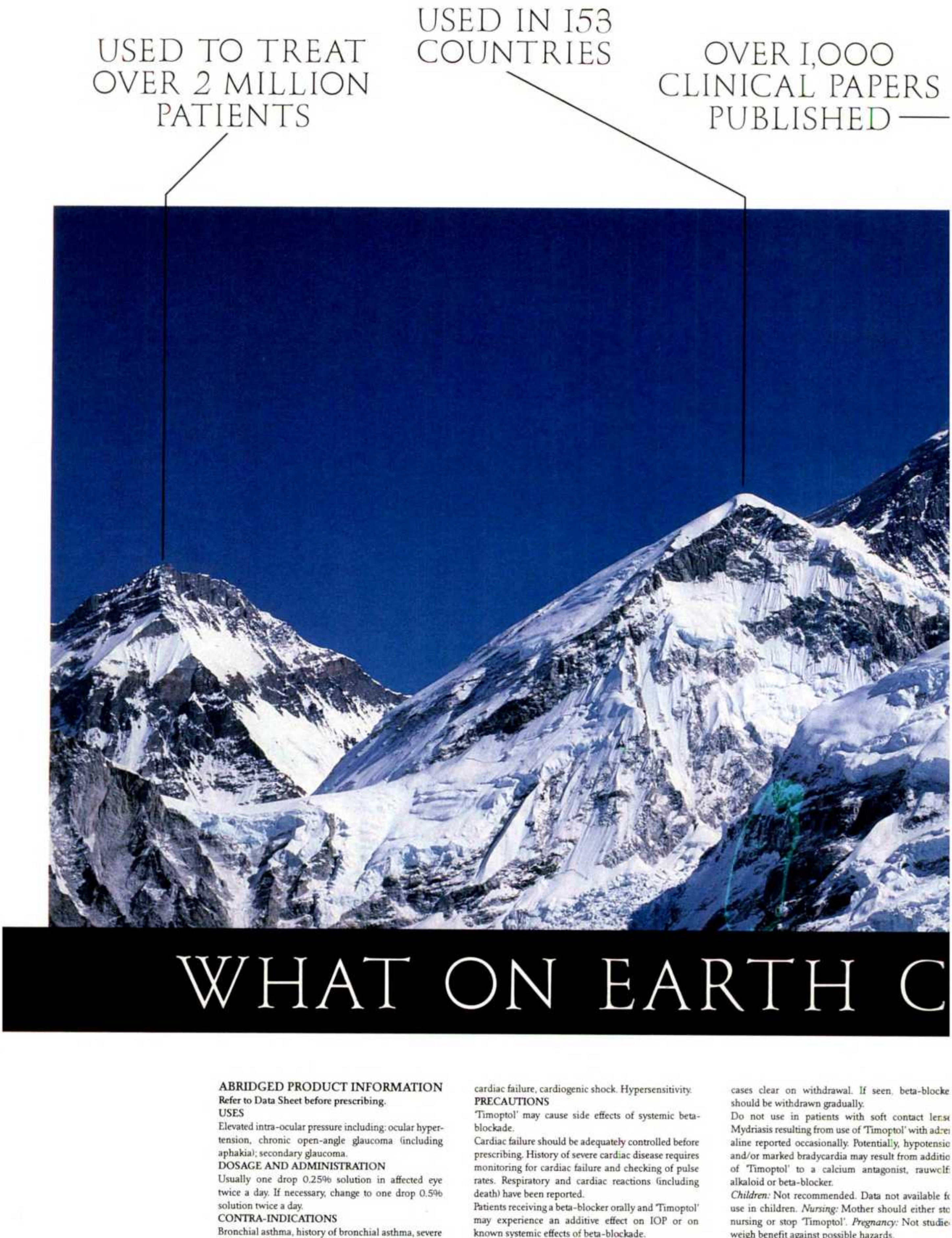
ONE DROP THEY WON'T FORGET

PRESCRIBING INFORMATION

RESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v). **ACTION:** Beta-adrenergic blocking agent. **INDICATIONS:** Reduction of traocular pressure in chronic open-angle glaucoma and ocular hypertension. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:** Contraindications: Bronchial thma; history of bronchial asthma; chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block; cardiac failure; cardiogenic ock; hypersensitivity to any component. Caution in labile diabetes and in patients receiving oral beta-adrenergic blocking agents. Do not use in patients continuing to wear ydrophilic (soft) contact lenses. Transient ocular burning and stinging on instillation may occur. Bradycardia, ypotension, dyspnoea and asthma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) nce or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE:** £5.05 L 0426/0060. Full prescribing information is available on request.

Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11.
Wandel, T. *et al.*, Am J Ophthalmol 1986; *101*: 298-304.

ALLERGAN PHARMACEUTICALS
Allergan Ltd., High Wycombe, Bucks HP12 3SH.
® Betagan is a registered trade mark.


USED TO TREAT OVER 2 MILLION PATIENTS
USED IN 153 COUNTRIES
OVER 1,000 CLINICAL PAPERS PUBLISHED —
WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blocke should be withdrawn gradually.

Do not use in patients with soft contact lense

Mydriasis resulting from use of 'Timoptol' with adre aline reported occasionally. Potentially, hypotensio and/or marked bradycardia may result from additio of 'Timoptol' to a calcium antagonist, rauwolf alkaloid or beta-blocker.

Children: Not recommended. Data not available fo use in children. *Nursing:* Mother should either sto nursing or stop 'Timoptol'. *Pregnancy:* Not studie weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, bleph

12-90 TOT.89.GB.4697.J.

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
PEN-ANGLE GLAUCOMA
ERAPY BY THE MAJORITY
UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE

TOP 'TIMOPTOL'?

is, keratitis, blepharoptosis, and decreased corneal sitivity. Visual disturbances, including refractory anges (due sometimes to withdrawal of miotics), lopia, and ptosis.
adycardia, arrhythmia, hypotension, syncope, art block, cerebrovascular accident, cerebral haemia, congestive heart failure, palpitation, rdiac arrest.
onchospasm (predominantly with pre-existing onchospastic disease), respiratory failure, dyspnoea.
adache, asthenia, nausea, dizziness, depression.
persensitivity, rash, and urticaria.
actions with an unestablished relationship are MO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST
0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack. 0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

Product licence numbers:
0.25% Ophthalmic Solution 'Timoptol', 0025/0134.
0.5% Ophthalmic Solution 'Timoptol', 0025/0135.
® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference
1. Data on file, Merck Sharp & Dohme Limited.

Ophthalmic Solution
Timoptol®
(timolol maleate, MSD)

NSURPASSED AS FIRST-LINE GLAUCOMA THERAPY

NIGHT WORKER.

Alcon's Maxitrol Ointment has been developed to provide the same highly effective action against inflammation and infection as Maxitrol drops but with an added benefit.

It is ideal for overnight use.

Consequently, a patient's sleep need not be disturbed, whether in hospital or at home, because Maxitrol goes on working through the night.

MAXIMISE
ON
MAXITROL®

Dexamethasone/Polymyxin B
Sulphate/Neomycin Sulphate

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford,
Herts, WD2 4YR.
Telephone: 0923 246133 Fax: 0923 243331

PRESCRIBING INFORMATION:

PRESENTATION: Dexamethasone Ph. Eur. 0.1% Polymyxin B Sulphate Ph. Eur. 6,000 units/g and Neomycin Sulphate Ph. Eur. equivalent to Neomycin 3.5mg/g in an ointment base. **CLINICAL USES:** Management of infectious ocular inflammations produced by organisms which are sensitive to Neomycin Sulphate and Polymyxin B Sulphate. Acute or chronic non-purulent conjunctivitis, blepharo-conjunctivitis, kerato-conjunctivitis, non-specific superficial keratitis, deep keratitis, and acne rosacea keratitis, herpes zoster ophthalmicus, iridocyclitis, mild acute iritis, recurrent marginal ulceration, corneal ulcer, non-purulent blepharitis, scleritis, episcleritis and sclero-conjunctivitis. Post-operatively to prevent ocular infection. **DOSAGE AND ADMINISTRATION:** Apply a small amount of ointment into the conjunctival sac, 3-6 times a day. When a favourable response is observed, the dosage may be reduced to 3-4 applications per day. This may be followed by once a day applications for several more days. **CONTRA-INDICATIONS:** This drug is contra-indicated in tuberculous, fungal and most viral lesions of the eye (herpes simplex/dendritic keratitis); vaccinia; varicella; acute purulent conjunctivitis and acute purulent blepharitis; and in those persons who have shown hypersensitivity to any of its components. **WARNINGS:** Extended use of topical therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If the condition does not respond within a reasonable period other forms of therapy should be instituted. Appropriate measures should be taken when this occurs. A few individuals may be sensitive to one or more components of this product. If any reactions indicating sensitivity are observed discontinue use. Extended use of topical steroids is a possible factor in the formation of subcapsular cataracts. **PREGNANCY WARNING:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long term treatment of pregnant patients. **LEGAL CATEGORY:** POM. **PACKAGE QUANTITY** 3.5g. **PRODUCT LICENCE NO:** 0649/5916.

British Journal of Ophthalmology, 1990, 74, 641–642

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Fluorosilicone oil for retinal detachment

The paper by Gremillion and colleagues on the use of fluorosilicone oil in the treatment of retinal detachment reintroduces the question of the role of the physical properties of silicone oil used in posterior segment surgery.

In the beginning Dow Corning manufactured a material called 360 Fluid Medical Silicone.[1] Its medical indications included the lubrication of plastic syringes and the coating of rubber catheters. Injection into human tissues was specifically excluded. This fluid was polydimethylsiloxane and was identical to laboratory grade 200 fluid silicone. Toxicological investigation prior to its use for these purposes had shown that silicone 360 caused little or no reaction when injected into tissues, so it was designated a 'medical fluid'.

Stone is credited with having been the first to inject silicone into the vitreous cavity of an animal.[2] In a now classic series of papers describing various forms of alloplasty in and around the eye he reported 'very little reaction' to liquid silicone injected into the rabbit vitreous after two years. Four years later Cibis published his early results in the human eye.[3]

Several years passed during which silicone was used by a small group of surgeons who developed the pioneering work of Cibis. Others learnt the techniques and developed them further, so that now in 1990 silicone is accepted as a valid technique in the treatment of complex vitreoretinal disease.

A wide variety of silicones have been used in vitreoretinal surgery, and some have been compared by Gabel and colleagues.[4] The decision to use a particular viscosity seems to have been based on commercial availability, the injecting system, and perhaps some consideration for theoretical advantage in the prevention of complications. Owing to the very wide variety of cases treated and marked differences in method and definition of complication it is difficult to draw any conclusions on the most suitable material to use at present.

Two principal varieties of silicone have been used as a retinal tamponade, polydimethylsilicone and fluorosilicone. The first has a density very slightly less than water and the second slightly greater. Thus fluorosilicone displaces water upwards in a two-phase mixture and should provide a more effective tamponade for inferior retinal breaks.

Dimethylsilicone has been used most widely as a long lasting tamponade following instrument membrane peeling in cases of proliferative retinopathy and giant retinal tear. The need for a tamponade in proliferative vitreoretinopathy relates to the underlying rhegmatogenous nature of this complication of retinal detachment, and in cases of giant tear to the need to maintain the posterior flap and retinal pigment epithelium in stable contact until the cryoadhesion becomes firmly established. Where inferior breaks exist, special care needs to be taken to ensure their adequate closure if the less dense material is employed.

When silicone became more widely used there was still uncertainty about the potential toxicity of the oil to the retina, so that it was removed in most cases. When the early toxicity experiments were repeated with controls who were operated upon[5] concern for the potential harmful side effects of silicone on the retina moved to the lens, and the cataract that often followed its use was attributed to some effect of silicone on metabolic transfer across the posterior surface of the lens.[6] Considerable doubt now exists that this is the case, with an increasing understanding of the global pathological changes which follow severe proliferative vitreoretinal disease.[7]

However, the most significant and unavoidable complication relating to the silicone oil itself remains, and that is what is called emulsification. At the present time it is the principle reason for recommending that silicone be removed wherever possible.

Gremillion and his coworkers had to remove their silicone very early – from two to eight weeks after surgery – because emulsification occurred in over 90% of cases. The redetachment rate following removal was nearly 25%, emphasising the very great difficulty which surrounds the decision to remove silicone in many patients. This dilemma underlines the importance of finding an answer to the question of foaming at the surface of silicone oil.

The possible relation between viscosity and emulsification has been investigated experimentally by Crisp and colleagues,[8] who found that low viscosity oils were more likely to emulsify than those with high viscosity. Viscosity is related closely to chain length and therefore to molecular weight, so that silicone oils with a homogeneous large molecular weight composition should be less likely to emulsify. The only report of the clinical use of very high viscosity silicone was from Constable, *et al.*,[9] who found no emulsification in a follow-up of three months to two years. They described some difficulty in injecting the oil, and no patient had the oil removed.

The apparent relationship between molecular weight and the risk of emulsification has led to the development of a new type of polydimethylsiloxane, which has been processed to remove low molecular weight fractions.[10] The fact that even high viscosity silicone oils contain significant amounts of short chain and cyclic fractions should allow the process of their removal to lead to less emulsification. Early personal experience with 1000 cSt new silicone has led to the conclusion that it has a high risk of severe early emulsification, whereas the 5000 cSt material is much less likely to emulsify and is acceptable. In Gremillion and coworkers' cases the fluorosilicone used for 28 out of 30 cases was 300 cSt viscosity only.

Analysis of 5000 cSt material removed from cases where emulsification has been a significant problem has shown that it has changed during or after injection (Burkhardt J, personal communication). This may lead to the possibility that the variation in presentation of emulsification may be due to the combination of the viscosity of the oil and the manner in which it is injected.

The need to remove cyclic siloxanes from the silicone oil may be important in the prevention of inflammation, since they are known to be toxic to the cornea[11] and might be harmful to the retina.[12] This can be done during the same manufacturing process which removes low molecular weight fractions and should further reduce doubts regarding the suitability of silicone oil for injection into the eye. However, it should be noted that there is no evidence that the presence of low molecular weight or catalyst residues is harmful to the retina. One report found a marked iris reaction when high viscosity fluorosilicone, which had been processed to remove low molecular weight components and catalyst residues, was injected into the vitreous of a vitrectomised rabbit eye.[13] There is however no evidence that these residues, if not removed, result in a more severe reaction using either dimethyl silicone or fluorosilicone.

The fact that there was a high incidence of emulsification after the use of fluorosilicone in Gremillion and co-workers' cases is probably the result of the use of low viscosity material. High viscosity homogeneous fluorosilicone can be manufactured,[13] though with more difficulty than with dimethyl silicone, and could provide a valuable high density fluid which would be effective in the tamponade of inferior breaks after vitrectomy.

Cibis in his earliest publication[3] reported the use of polydimethylsiloxane and fluorosilicone in rabbit eyes and found no difference in response. This might encourage us to look for alternative material with differing physical properties to extend our surgical range in the treatment of complex vitreoretinal disease.

At present it would seem prudent to use 5000 cSt polydimethyl silicone oil prepared for specific use within the eye. Anything else might expose the surgeon to potential medicolegal complications which, despite existing lack of hard evidence, might be difficult to defend.

J D SCOTT

1 Dow Corning 360 Medical Fluid Technical specification 9 May 1966
2 Stone W. Medical progress Alloplasty in surgery of the eye. *N Engl J Med* 1958; 258: 486–90
3 Cibis P. The use of liquid silicone in retinal detachment surgery *Arch Ophthalmol* 1962; 68: 590–9.
4 Gabel V-P, Kampik A, Burghardt J. Analysis of intraocularly applied silicone oils of various origins. *Graefes Arch Clin Exp Ophthalmol* 1987; 225: 160–2.
5 Ober R, Blanks J, Ogden T, Pickford M, Minckler D, Ryan S. *Retina* 1983, 3: 77–85.
6 Lucke K, Laqua H. *Silicone oil in the treatment of complicated retinal detachments.* New York, Heidelberg Springer, 1990· 102
7 Scott J Lens epithelial proliferation in retinal detachment *Trans Ophthalmol Soc UK* 1982; 102: 385–9.
8 Crisp A, de Juan E, Tiedman J. Effect of silicone oil viscosity on emulsification *Arch Ophthalmol* 1987, 105: 546–50
9 Constable I, Mohamed S, Tan P. Super viscous silicone liquid in retinal surgery *Aust J Ophthalmol* 1982; 10: 5–11.
10 Adatomed Technical specifications. Silicone oil Op 1000/Op 5000. 1986.
11 Refojo M, Roldan M, Leong F-L, Henriquez A Effect of silicone oil on the cornea *J Biomed Res* 1985; 19: 643–52
12 Gabel V-P Polydimethylsiloxane and the factors influencing its intraocular biocompatibility. In Heimann K, Wiedmann P, eds *Proliferative vitreoretinopathy*. Heidelberg: Kaden, 1989· 156
13 Gabel V-P, Kampik A, Gabel C, Spiegel D Silicone oil with high specific gravity for intraocular use. *Br J Ophthalmol* 1987, 71: 262–7

British Journal of Ophthalmology, 1990, 74, 643–646

ORIGINAL ARTICLES

Fluorosilicone oil in the treatment of retinal detachment

Charles M Gremillion Jr, Gholam A Peyman, Kwan-Rong Liu, Khaled S Naguib

LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, LA, USA
C M Gremillion Jr
G A Peyman
K-R Liu
K S Naguib

Correspondence to:
Gholam A Peyman, MD,
LSU Eye Center, 2020 Gravier Street, Suite B, New Orleans, LA 70112, USA

Accepted for publication
23 May 1990

Abstract

We evaluated the use of a heavier-than-water fluorinated silicone oil in the treatment of 30 selected cases of complicated retinal detachment from January 1988 to July 1989. Proliferative vitreoretinopathy grade C-2 or greater accounted for 19 cases, proliferative diabetic retinopathy with traction detachment for two cases, giant retinal tears five, ruptured globe with retinal detachment two, massive choroidal effusion with retinal detachment one, and acute retinal necrosis with retinal detachment one. Initial retinal reattachment was achieved in all cases. Complications included redetachment seven (23%), cataract six (75% of phakic patients), raised intraocular pressure four (13%), hypotony four (13%), keratopathy three (10%), uveitis-synechia formation three (10%), phthisis two (3%), choroidal haemorrhage one (3%), and vitreous haemorrhage one (3%). Postoperative visual acuities with at least six months' follow-up range from no light perception to 20/50, with seven patients (23%) 20/400 or better.

Since its introduction by Cibis *et al* in 1962[1] silicone oil has proved useful in the repair of complicated retinal detachment. It is relatively transparent and provides retinal tamponade for longer periods than intraocular gases. Conventional silicone, with a specific gravity of 0·9 g, floats on the surface of intraocular fluids, producing its most effective retinal support in the superior quadrants.[2] We evaluated a fluorinated, heavier-than-water (specific gravity of 1·35 g) silicone oil[3] in 30 patients with retinal detachment. This property could eliminate the need for posterior retinotomy by allowing subretinal fluid to be drained through peripheral retinal breaks and could simplify repair of giant retinal tears.[4-7] We also evaluated its usefulness in retinal support in the inferior quadrants, an area of the retina exposed to intraocular fluid following gas or conventional silicone placement and the commonest site for the development of proliferative vitreoretinopathy (PVR).

Materials and methods

From January 1988 to July 1989 we used high specific gravity fluorosilicone oil (FSO) in the repair of complicated retinal detachment in 30 selected cases (Tables 1 and 2). Ages ranged from 11–79 years with 20 males and 10 females. Rhegmatogenous retinal detachment with significant PVR accounted for 19 cases, proliferative diabetic retinopathy with traction detachment for two, giant retinal tears five, ruptured globe with retinal detachment two, massive choroidal

Table 1 Fluorosilicone cases

Case	Age/ sex	Nature of RD	Preop visual acuity	Time to FSO removal (weeks)	Follow-up (months)	Postop visual acuity
1	11 M	PVR-D_2 aphakic	HM	8	12	HM
2	47 M	PVR-D_1	HM	8	12	HM
3	33 M	Giant tear	HM	IO	12	HM
4	36 M	PVR-D_1, ectopia lentis	CF	6	11	20/400
5	51 M	PDR	CF	7	7	HM
6	52 M	PVR-D_1	HM	6	10	CF
7	35 M	PVR-D_1, aphakic	CF	8	7	CF
8	26 F	Giant tear	CF	IO	7	20/200
9	21 M	PVR-D_2	HM	8	5	LP
10	55 F	PVR-D_2, aphakic	HM	8	4	CF
11	43 M	PDR	CF	8	3	LP
12	59 F	PVR-D_1	HM	8	4	HM
13	26 F	Blunt trauma, ruptured globe, VH, RD	LP	3	3	HM
14	14 F	PVR-D_2	HM	3	3	HM
15	73 M	PVR-D_3	LP	6	10	HM
16	64 M	PVR-C_3	HM	4	9	CF
17	79 M	PVR-D_2	HM	5	6	LP
18	27 M	PVR-D_2	HM	3	6	CF
19	49 M	Ruptured globe, choroidals, VH, RD	LP	3	6	NLP
20	36 M	PVR-C_1	20/200	4	10	HM
21	49 M	PVR-D_2	HM	5	8	HM
22	53 M	PVR-D_1	CF	6	6	LP
23	39 M*	Giant tear	CF	7	7	CF
24	31 F*	Giant tear, macular hole	20/200	4	11	20/100
25	16 F	Dialysis PVR-B_1	20/400	2	6	20/100
26	30 M	PVR-C_1	CF	6	9	20/70
27	53 M	PVR-C_3	HM	4	10	HM
28	11 F	Giant tear	LP	3	10	CF
29	72 F	Massive choroidal effusion	HM	3	6	20/50
30	26 F	Acute retinal necrosis	CF	3	6	20/200

*1000 cSt (=mm^2/s) fluorosilicone
CF=counting fingers. VH=vitreous haemorrhage HM=hand motion RD=retinal detachment LP=light perception IO=intraoperatively. PVR=proliferative vitreoretinopathy PDR=proliferative diabetic retinopathy.

Table 2 Preoperative profile, fluorosilicone cases

Rhegmatogenous	19
PVR C_1 3	
C_2 1	
C_3 2	
D_1 6	
D_2 6	
D_3 1	
Proliferative diabetic retinopathy	2
Giant tear	5
Ruptured globe with retinal detachment	2
Massive choroidal effusion	1
Acute retinal necrosis with retinal detachment	1
Total	30

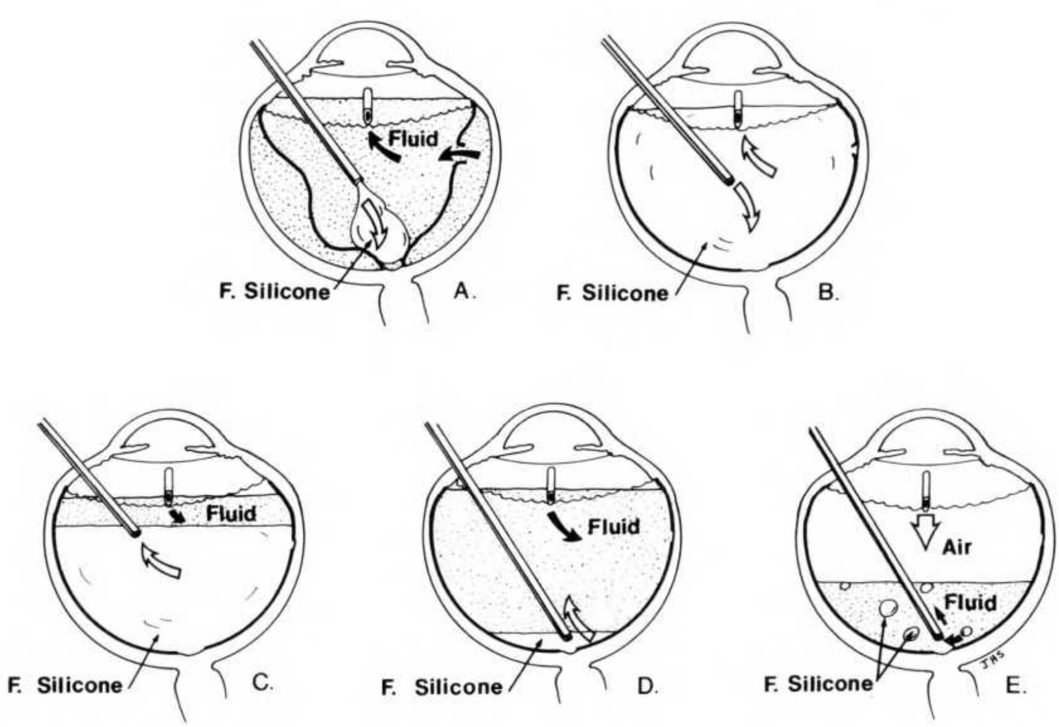


Figure 1 Fluorosilicone oil injection. (A) The oil is injected near the optic disc. Consequently, subretinal fluid is drained through the peripheral retinal break. (B) As more oil is injected, the retina is completely flattened and all subretinal fluid is drained. Fluorosilicone oil removal: (C and D) The extrusion needle is kept below the ingoing fluid level. (E) Repeated air/fluid exchange is performed to obtain complete fluorosilicone oil removal.

effusion ('kissing choroidals') with retinal detachment one, and acute retinal necrosis with retinal detachment 1. The decision to use FSO was based on the size and location of retinal break (peripheral to the equator), degree of PVR (15 cases C_2 or worse),[8] or the need for posterior/inferior tamponade. Nineteen patients had had previous surgical attempts at repair of retinal detachment (Table 2).

PROCEDURE

Rectus muscles were isolated and tagged in standard fashion and an infusion cannula was placed through a sclerotomy 4·0 mm from the limbus (phakic) or 3·5 mm (aphakic). Pars plana vitrectomies or revision of prior vitrectomies were performed on all patients through sclerotomies in the superonasal and superotemporal quadrants. Epiretinal membrane dissection and relaxing retinotomies were performed when necessary. After mobilisation of the retina was complete, FSO was injected through a 20-gauge cannula via a 12 ml syringe (Fig 1A, B). The cannula tip was held posteriorly over the optic nerve and the FSO (3·5 to 4·0 ml) slowly injected, forcing the subretinal fluid peripherally and eventually out the peripheral breaks. Endophotocoagulation and peripheral retinal cryopexy were applied where indicated. Scleral buckling or revision of existing buckles was performed in 29 of 30 cases (all except case 29). Fluorosilicone oil was aspirated or injected via the infusion cannula to establish intraocular pressure between 15 and 20 mmHg. Copious irrigation of the surgical field was performed to remove FSO from the ocular surface, and the conjunctiva was closed in standard fashion. In two cases 1000 cSt (1000 mm^2/s) FSO was used, and 300 cSt (300 mm^2/s) FSO was used in the remaining 28 (Table 1).

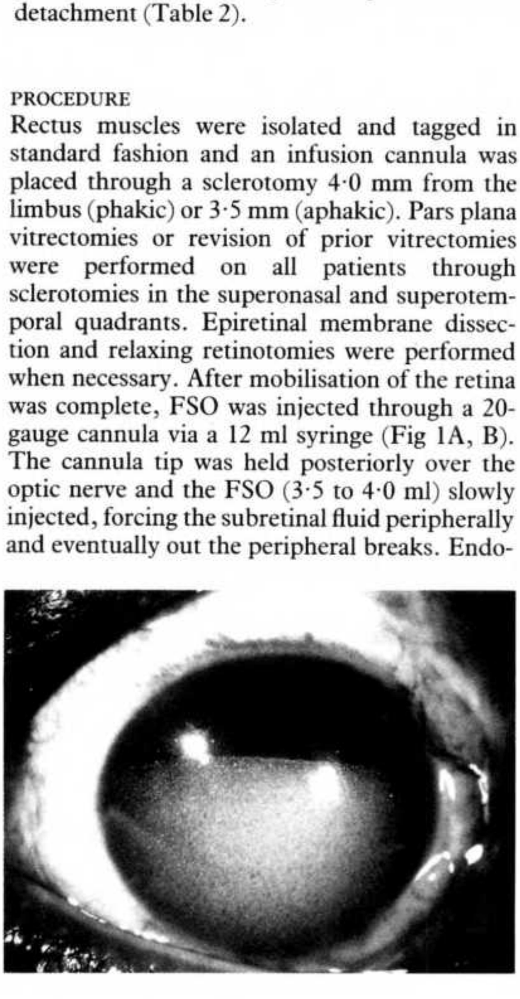


Figure 2 Emulsified FSO occupying two-thirds of the anterior chamber.

TIMING AND TECHNIQUE OF FLUOROSILICONE OIL REMOVAL

Fluorosilicone oil was removed from all eyes two to eight weeks after its insertion. The determination to remove FSO was based primarily on emulsification. Although strict grading of the degree of emulsification was not recorded, fluorosilicone oil was removed in early cases (1 and 2) when retinal details became obscured by emulsification and in later cases when the first signs of emulsification were observed (Fig 2).

Removal was performed under general anaesthesia in 29 cases (all except case 30). An infusion cannula was placed and sclerotomies performed as for standard pars plana vitrectomy. Balanced salt solution (BSS plus) was used as an infusion fluid.

In cases 23 and 24, where high viscosity FSO was used (1000 cSt=mm^2/s) a powerful aspiration source was necessary to evacuate the substance adequately. An 18 gauge blunt cannula was attached to flexible tubing affixed to a 50 ml syringe. The cannula was directed by the surgeon using endoillumination and microscopic visualisation. The aspiration was performed by an assistant with retraction of the syringe plunger. The process was carried out until all visible FSO was removed.

In the remaining 28 cases, in which 300 cSt (=mm^2/s) FSO was used, aspiration was possible by means of standard vitrectomy aspirating equipment (microvit, vitrophage) connected to a blunt 20 gauge cannula (Fig 1C, D). The fluorosilicone oil was aspirated until all visible FSO was removed. In cases where FSO was present in the anterior chamber of phakic and pseudophakic patients a limbal incision was performed, and the FSO was aspirated via the above system.

After removal of all visible FSO repeated air-fluid exchange was performed (Fig 1E). This manoeuvre resulted in additional accumulation of FSO posteriorly, which was removed by the above aspiration technique. Air-fluid exchange was performed two to three times in each patient. The eye was filled with the infusion fluid after all FSO appeared to be removed. The infusion cannula was removed, and sclerotomies and conjunctiva were closed in standard fashion.

Results

Intraoperative retinal reattachment was achieved in all cases. Relaxing retinotomy was required in nine of 30 cases. Retinal detachment recurred in seven cases (23%), three of which occurred at the time of FSO removal (cases 16, 21, 30). These were limited and appeared to occur from undetected breaks on the posterior slope of the scleral buckle. They were repaired during the same operation by standard air-fluid exchange and injection of conventional silicone oil. In three cases the retina beame detached after FSO removal as a result of PVR. Two of these cases required reattachment procedures with injection of conventional silicone oil. One case was deemed inoperable, and the remaining case had a limited detachment not involving the macula and has remained unchanged for four months.

In cases of giant tears, injection of FSO over the optic disc produced immediate flattening of the posterior retina, with extrusion of subretinal fluid out of the peripheral break. With additional FSO injection the entire retina was reattached from posterior to anterior.

Postoperative visual acuities ranged from no light perception (NLP) to 20/50 (Table 1, Fig 3). Fourteen patients (47%) showed improvement of one line or more while seven (23%) lost one line or more. Nine patients remained unchanged.

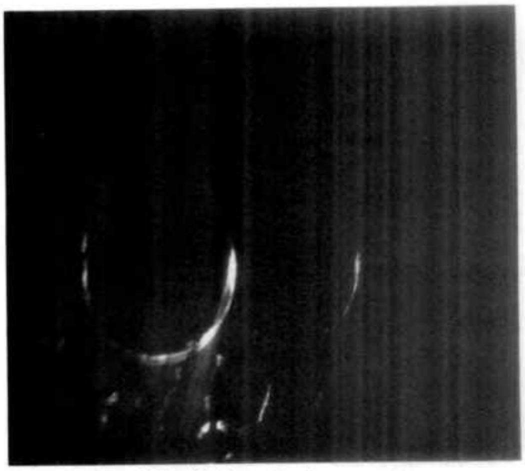


Figure 4 Emulsified FSO in the vitreous cavity.

Emulsification of FSO occurred as early as one week after injection (case 25) and was present in all cases at the time of FSO removal (Figs 4, 5, Table 3). Significant emulsification (obscuring retinal details) occurred in eight patients. The two cases in which FSO was removed during the initial procedure were excluded when calculating the rate of occurrence of this complication (Table 3).

Cataract formation occurred in six of eight phakic patients. These were posterior subcapsular in nature. A raised intraocular pressure was detected in four patients and was treated with topical and oral antiglaucoma medications. Hypotony (intraocular pressure less than 6 mmHg) occurred in four patients. Marked intraocular inflammation and synechia formation between iris and lens capsule or intraocular lens was present in three eyes (all were also hypotonus and included above).

Keratopathy, defined as corneal thickening or oedema detected by slit-lamp examination in the absence of raised or reduced intraocular pressure, was present in three eyes and resolved after removal of FSO (Fig 5). One eye (case 19) developed postoperative choroidal haemorrhage and became phthisical.

Discussion

Heavier-than-water vitreous replacement substances have been used with variable results.[9-12]

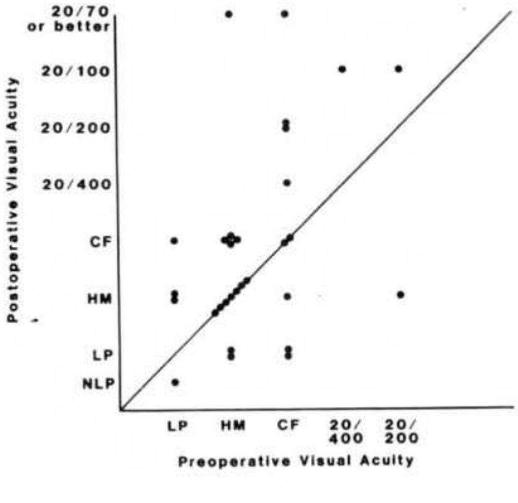


Figure 3 Preoperative, postoperative visual acuities. CF – counting fingers. HM – hand motion. LP – light perception. NLP – no light perception.

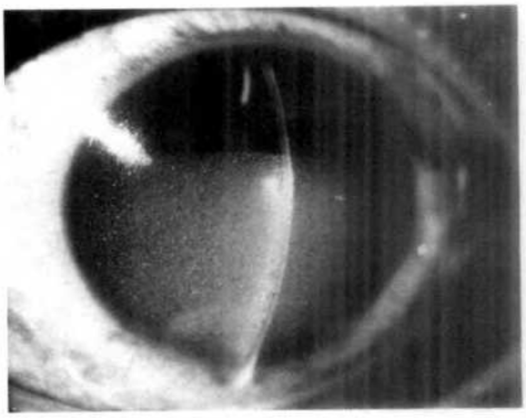


Figure 5 Slit lamp photograph showing increased corneal thickness with FSO filling two-thirds of the anterior chamber.

Table 3 Postoperative complications (n=30)

Emulsification*	28	(93%)
PVR	8	(26%)
Redetachment	7	(23%)
Cataract†	6	(75%)
Retinal breaks	5	(18%)
Raised IOP	4	(13%)
Hypotony	4	(13%)
Uveitis/synechiae	3	(10%)
Keratopathy	3	(10%)
Phthisis	2	(3%)
Choroidal haemorrhage	1	(3%)
Vitreous haemorrhage	1	(3%)

*n=28
†n=8

The theoretical advantages of the higher specific gravity materials are (1) draining subretinal fluid via a peripheral break and eliminating the need for posterior retinotomy; (2) obviating the need for inverting the patient or a complicated technique in repair of giant tears; (3) maintenance of postoperative retinal tamponade in the inferior quadrants; (4) post-operative supine positioning; and (5) long-term retinal tamponade. Our study suggests that four of these objectives can be achieved with FSO.

In patients with peripheral retinal breaks (including giant tears) subretinal fluid was easily removed by injecting FSO posteriorly over the optic disc and allowing the fluid to exit via the break and through the infusion cannula or sclerotomy site.

Inferior retinal tamponade can be maintained postoperatively for three to four weeks. In our hands considerable emulsification occurred after this period, rendering the FSO less efficient and complicating the removal. This emulsification was variable and appeared to relate to the patients' level of activity; however, this could not be statistically correlated. A higher viscosity FSO may reduce emulsification, but its removal is very difficult.[13]

As described above the 1000 cSt (=mm^2/s) FSO was removed by creating suction with a 50 ml syringe connected via tubing to an extrusion cannula. Intense and continuous retraction on the plunger was required to remove the oil at a very slow rate. Approximately one hour of actual aspiration time was required. Removal of 300 cSt (=mm^2/s) FSO was quite easily done with a standard extrusion needle.

Postoperative supine positioning was used in all patients, often with the head slightly elevated. Long-term tamponade was not satisfactorily achieved, as emulsification obscured retinal details and led to other complications previously discussed.

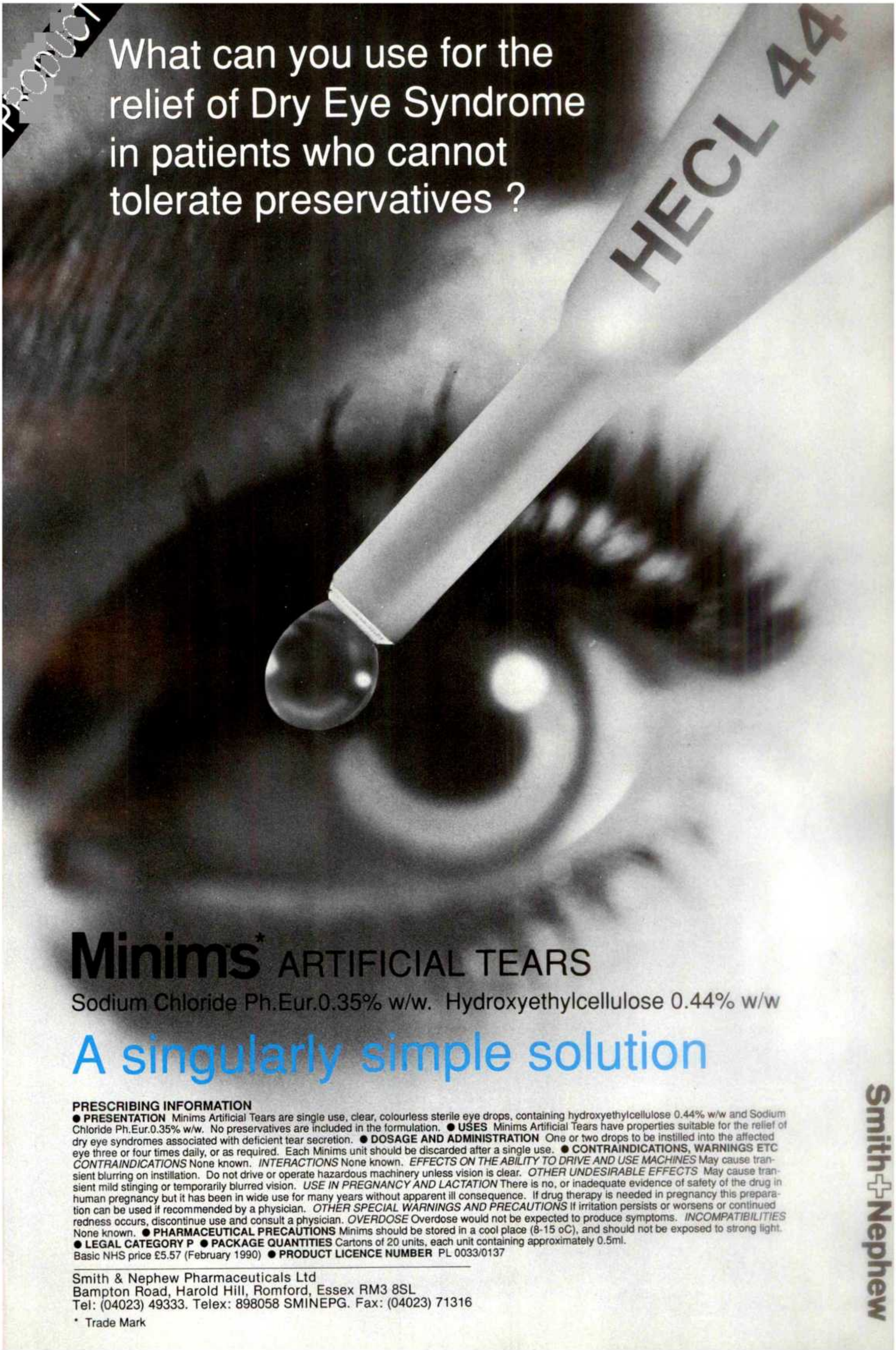
Complications of raised intraocular pressure, and keratopathy, were managed medically and resolved with removal of FSO. Cataract formation was high (six of eight phakic eyes), and the subsequent removal by extracapsular technique led to marked intraocular inflammation. Three of these eyes were included in 'uveitis/synechia' as synechiae formed between the iris-intraocular lens or iris-lens capsule. Two of these eyes became hypotonus (IOP ≤ 6). It is our impression that FSO may alter the blood-ocular barrier, which gives rise to a marked inflammatory response if subsequent surgery is performed on the anterior segment. Surprisingly, this inflammatory response was not observed in patients requiring an additional posterior segment operation.

Though retinal reattachment was achieved in all cases, redetachment occurred in seven (23%). Three of these were rhegmatogenous and appeared to result from previously undetected breaks on or near the posterior slope of the buckle. Reattachment was achieved in five of these cases with repeat surgery and injection of conventional silicone oil.

Our series demonstrates that FSO can be used as an intraoperative tool to facilitate repair of complicated retinal detachment and to provide retinal support in the inferior quadrants. Complications are similar to those reported with conventional silicone oil.[14-16] However, our observation of marked inflammation following anterior segment surgery in three patients is of concern and warrants further evaluation. FSO may prove useful as an intraoperative tool or intermediate vitreous replacement as the evaluation and search for a more permanent heavier-than-water substitute continues.

This work was supported in part by US Public Health Service grants EY07541 and EY02377 from the National Eye Institute, the National Institutes of Health Services, Bethesda, MD, USA.

1 Cibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery *Arch Ophthalmol* 1962; 68: 590–9
2 McCuen BW, de Juan E Jr, Landers MB, Machemer R Silicone oil in vitreoretinal surgery Part 2 Results and complications. *Retina* 1985, 5: 198–205.
3 Miyamoto K, Refojo MF, Tolentino F, Fournier GA, Albert DM. Fluorinated oils as experimental vitreous substitutes. *Arch Ophthalmol* 1986, 104: 1053–6
4 Liu KR, Peyman GA, Miceli MV Experimental evaluation of low viscosity fluorosilicone oil as a temporary vitreous substitute. *Ophthalmic Surg* 1989; 20: 720–5
5 Peyman GA, Smith T, Charles H Injection of fluorosilicone oil and pars plana vitrectomy for complex retinal detachment *Can J Ophthalmol* 1987, 22: 276–8
6 Peyman GA, Smith RT Use of fluorosilicone to unfold a giant tear *Int Ophthalmol* 1987; 10: 149–51
7 Paylor R, Peyman GA, Badri S Effects of intravitreal injection of fluorosilicone oil after vitrectomy in the rabbit eye *Can J Ophthalmol* 1987, 22: 251–3.
8 Retina Society Terminology Committee. The classification of retinal detachment with proliferative vitreoretinopathy. *Ophthalmology* 1983; 90: 121–5.
9 Chang S Low viscosity liquid fluorochemicals in vitreous surgery *Am J Ophthalmol* 1987, 103: 38–43.
10 Chang S, Zimmerman NJ, Iwamoto T, Ortiz R, Faris D Experimental vitreous replacement with perfluorotributylamine. *Am J Ophthalmol* 1987, 103: 29–37
11 Miyamoto K, Refojo MF, Tolentino FI, Fournier GA, Albert DM. Perfluoroether liquid as a long term vitreous substitute *Retina* 1984; 4. 264–8.
12 Biro GP, Blais P Perfluorocarbon blood substitutes *CRC Crit Rev Oncol Hematol* 1987; 6: 311–74
13 Crisp A, de Juan E Jr, Tiedeman J Effect of silicone oil viscosity on emulsification *Arch Ophthalmol* 1987, 105: 546–50
14 Labelle P, Okun E Ocular tolerance to liquid silicone. an experimental study *Can J Ophthalmol* 1972; 7: 199–204
15 Nabih M, Peyman GA, Clark LC Jr, *et al* Experimental evaluation of perfluorophenanthrene as a high specific gravity vitreous substitute a preliminary report *Ophthalmic Surg* 1989, 20: 286–93
16 Leaver PK, Grey HB, Garner A Silicone oil injection in treatment of massive preretinal retraction II. Late complications in 93 eyes. *Br J Ophthalmol* 1979, 63: 361–7



What can you use for the
relief of Dry Eye Syndrome
in patients who cannot
tolerate preservatives ?

Minims* ARTIFICIAL TEARS

Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

A singularly simple solution

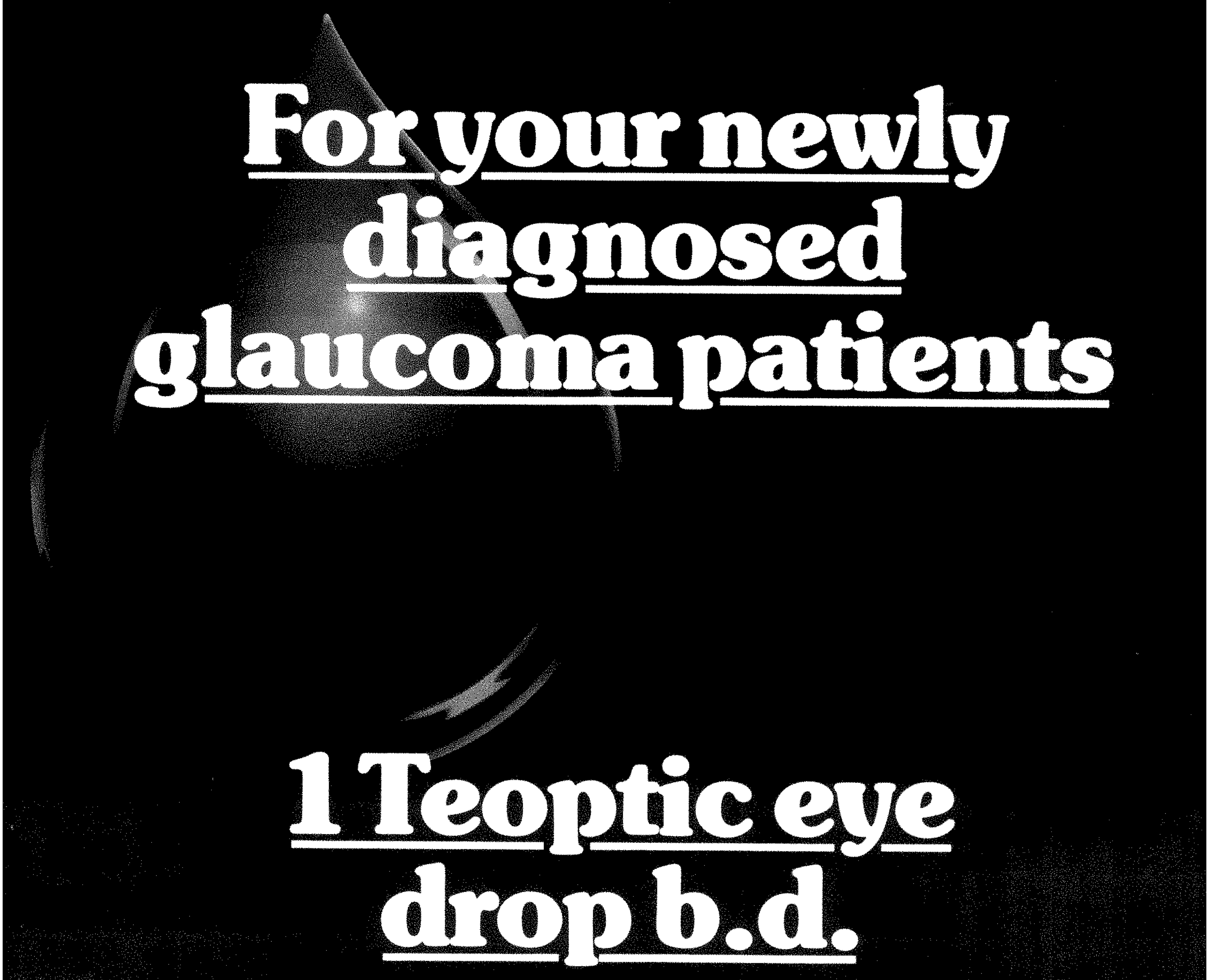
PRESCRIBING INFORMATION

● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml.
Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

* Trade Mark

Smith+Nephew



References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10,** 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85,** 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105,** No.2, 150-154.

Teoptic: Abbreviated prescribing information
Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity. **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

- Effectively lowers IOP [1]
- Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol * [2,3]
- Has a prolonged therapeutic effect [4] thus offering flexible b.d. dosage regimen
- Well tolerated with few local side-effects [5]
- Low concentration of benzalkonium chloride in a buffered solution.

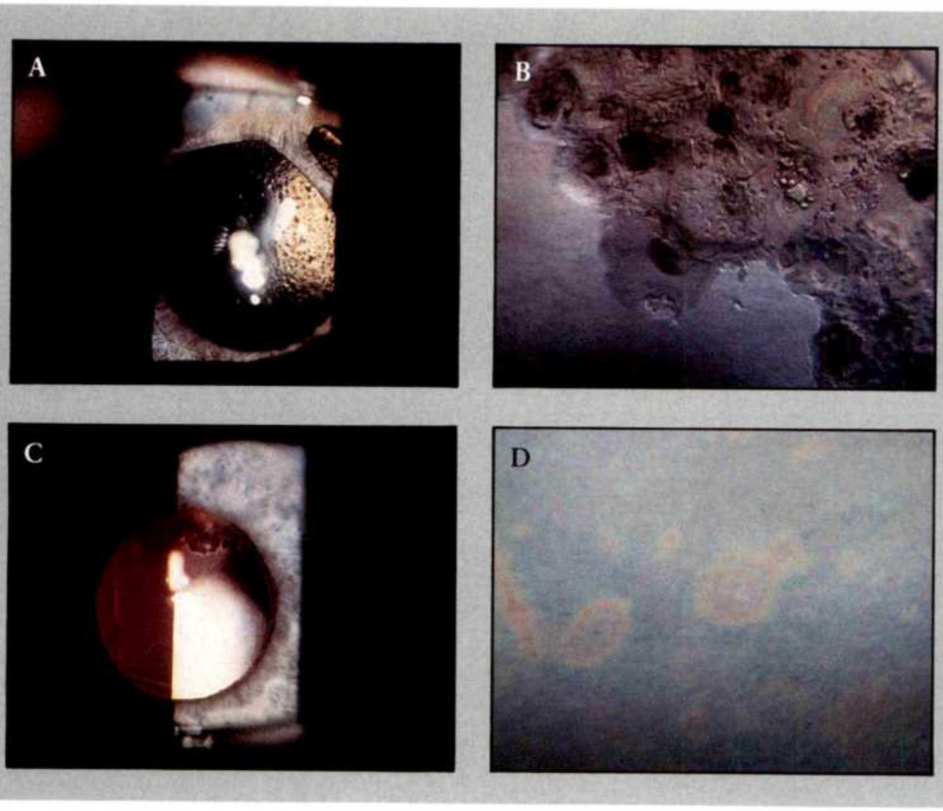
*** Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.**

Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.
Teoptic is under licence from Otsuka, Japan.

Further information is available on request to the above address.

Comparison between Heparin surface modified IOLs and normal IOLs in the same patient.



This female has a history of longstanding diabetes and glaucoma.

A. Slit lamp
B. Specular microscopy

Right eye — NORMAL PMMA LENS

- 11 months post-operativel
- Confluent giant cells can seen clearly on both slides

C. Slit lamp
D. Specular microscopy

Left eye — HEPARIN SURFACE MODIFIED LEN

- 6 months post-operatively
- No giant cells
- Newton's rings seen clearl

A clear case for Heparin surface modified IOLs.

Pharmacia Limited,
Ophthalmics Division, Pharmacia House, Midsummer Boulevard, Milton Keynes MK9 3HP.
Telephone: (0908) 661101. Telex: 826778. Fax: (0908) 690091

Pharmaci

Intraocular pressure changes and postural changes of intraocular pressure in experimentally induced Hansen's disease of rhesus, mangabey, and African green monkeys

Naushad Hussein, Bruce Ostler, Bobby J Gormus, Robert Wolf, Gerald P Walsh

Francis I Proctor Foundation, University of California, San Francisco, CA 94143, USA
N Hussein
H B Ostler

Delta Regional Primate Research Centre, Covington, Louisiana 70433, USA
B J Gormus

DVM University of Texas, San Antonio, Texas, USA
R Wolf

Leonard Wood Memorial Laboratory for Leprosy Research, Cebu, Phillipines
G P Walsh

Correspondence to:
H Bruce Ostler, MD,
FI Proctor Foundation,
University of California, San Francisco, CA 94143–0944, USA

Accepted for publication
2 February 1990

Abstract

In our long term evaluation of patients with Hansen's disease we have frequently found reduction of their intraocular pressure. Furthermore, we noted changes in their intraocular pressure on change of posture. To determine if these changes have any significance we measured the intraocular pressures of 24 experimentally infected and 39 control monkeys in both sitting and reclining positions. We found significant reduction of intraocular pressure in 66·7% compared with controls in the sitting position, and a significant increase in intraocular pressure in 79% when checked first in the sitting then in the reclining position. We offer a possible pathophysiological explanation as to why the changes occur.

Ocular complications are common in Hansen's disease. Our clinical observations show that in many patients (even younger patients, patients without other evidence of ocular diseases, and patients with disease for only a short period), early ocular involvement probably occurs as shown by decreased intraocular pressure and a significant change in pressure with a change in posture.[1]

To evaluate the significance of intraocular pressure changes we examined the external eyes of 24 monkeys (mangabey, rhesus, and African green) which had been inoculated with *Mycobacterium leprae* organisms. We measured their intraocular pressures in a sitting and reclining position. Many of the animals had developed typical skin and peripheral nerve lesions at the time of the examination. We also examined a group of control monkeys in a similar fashion.

Table 1 Experimental group: dose, site, and date of inoculation

	M mulatta (rhesus monkey)	*C atys (mangabey monkey)*	*C aethiops (African green monkey)*
Sex	Male 8	Male· 8	Male: 5 Female 3
Age (mean)	2 3 years	9 9 years	6·2 years
Dose	$2{\cdot}3\times10^{7}$	$1\ 8\times10^{5}$	$1\ 1\times10^{7}$
(range)	$1{\cdot}6\times10^{8}$	$3{\cdot}3\times10^{7}$	$8\ 0\times10^{10}$
Site of inoculation	IV/IC	IV/IC	IV/IC/ID
Date of inoculation	Aug 1986	Feb 1984	May 1981
(range)	Sept 1986	Dec 1985	Jan 1987

Dose=number of organisms. IV=intravenous, ID=intradermal; IC=intracutaneous.

Table 2 Control group: intraocular pressure observations

Species	*Clinical Disease*	*Nasal AFB*	*RX*	*IOP Mean (SD) mmHg (S)*	*(C)*
M mulatta (rhesus) n=13	0/13	0/13	0/13	15 08/15·08 (1·59/1 73)	1 08/1 31 (1·38/1·32)
C aty (mangabey) (n=13)	0/13	0/13	0/13	14·54/14·65 (2 56/2·61)	1·08/1 00 (1 00/0 78)
C aethiops (African green) n=3	0/13	0/13	0/13	17 54/18·00 (1 28×1 80)	1·54/1 62 (1·39/1 21)

Nasal AFB=nasal scrapings positive for acid fast bacilli RX=combination of rifampin with/without dapsone given for clinical disease IOP Mean (S)=mean sitting intraocular pressure IOP mean (C)= mean postural change in intraocular pressure SD=standard deviation

Materials and methods

We examined both eyes of 24 experimentally infected and 39 control (uninfected) monkeys with a Zeiss hand held slit-lamp, and a Kawo HA-1 hand held applanation tonometer which had been previously calibrated and correlated with a mounted Goldmann applanation tonometer.

The experimentally infected monkeys consisted of eight *Macaca mulata* (rhesus monkeys), eight *Cerocebus atys* (sooty mangabey monkeys), and eight *Cercopithecus aethiops* (African green) monkeys. The control group consisted of 13 mangabey, 13 African green, and 13 rhesus monkeys. The experimentally infected monkeys had been inoculated with *M. leprae* from different sources, at different times and at different sites (Table 1). Control monkeys were unexposed, uninoculated, and housed in separate quarters. Data on each monkey from the time of admission to the Delta Primate Center until the time of our examination were obtained from a log kept on each monkey. The data included time and mode of inoculation (Table 1), observations of each animal (Table 2), results of nasal smears examined for acid fast bacilli (Table 2), and treatment.

The monkeys were examined under neuroleptic anaesthesia obtained by administration of intramuscular ketamine. Following examination with the slit-lamp one drop of 0·4% benoxinate HCl and 0·25% flurorescein Na was instilled into the inferior fornix of each eye, the excess wiped from the eyelids with clean tissue paper, and the intraocular pressures measured in both the sitting and reclining positions. The monkeys were held by an assistant in the sitting position while the intraocular pressures of each eye were measured and recorded in mmHg under (S= sitting). The monkeys were then placed flat on their backs, and the pressure measured in each eye and recorded in mmHg under (L=lying). The postural changes were later calculated and are listed in the tables as (C=change). Random multiple intraocular pressure readings were measured on selected monkeys of both groups in

Table 3 Experimental group: intraocular pressure observations

Species	*Clinical Disease*	*Nasal AFB*	*RX*	*IOP Mean (SD)*	*mmHg*
				(S)	*(C)*
M mulatta (rhesus) n=8	2/8	1/8	0/8	9·50/10·38 (4·02/3·31)	5·25/3·87 (3·36/3·44)
C aty (mangabey) n=8	8/8	6/8	3/8	9·75/9·75 (4·63/6·77)	5·87/9·00 (4·28/6·76)
C aethiops (African green) n=8	1/8	0/8	0/8	7·25/6·63 (3·11×3·57)	6·88/8·25 (2·71/2·91)

the sitting and reclining positions. The readings were reproducible and the changes immediate and persistent.

Results

Control group (Table 3). The mean intraocular pressure (IOP) in the 13 mangabey monkeys while sitting was (OD/OS) 14·54/14·65 mmHg (SD 2·56/2·61); in the 13 rhesus monkeys the mean intraocular pressure while sitting was (OD/OS) 15·08/15·08 mmHg (SD 1·59/1·73); and in the 13 African green monkeys the mean intraocular pressure was (OD/OS) 17·54/18·00 mmHG (SD 1·28/1·80). The mean postural change (lying – sitting=change) in the mangabey monkeys was 1·08/100 mmHg (SD 1·00/0·78); in the rhesus monkeys the change was 1·08/1·31 mmHg (SD 1·38/1·32) and in the African green monkeys it was 1·54/1·62 mmHg (SD 1·39/1·21).

Experimental groups. All three species of inoculated/infected monkeys had a significantly lower sitting intraocular pressure and significant postural changes (elevation of pressure when in the reclining position). Asymmetry of intraocular pressure was also observed in all inoculated monkeys. At the same time we could not detect evidence of external disease. Specifically, we looked for evidence of keratitis, corneal nerve beading, episcleritis, scleritis, iritis, and cataracts. Two monkeys as noted below, however, had conjunctival granulomas.

Rhesus monkeys. Four of the eight monkeys in the rhesus group were inoculated eight months before our examination, the other four nine months before. The mean age was 2·3 years. Clinical lesions at dermal inoculation sites were present in one monkey after four months and one other monkey after eight months. The others were free of clinical disease. In this group of monkeys the mean intraocular pressure (S) was 9·5/10·38 mmHg (SD 4·02/3·31), and the mean postural change in intraocular pressure (C) was 5·25/3·87 mmHG (SD 3·36/3·44).

Mangabey monkeys. There were two subgroups of mangabey monkeys. One group had a mean age of 13·1 years and had been inoculated 40 months before our examination. The other group had a mean age of 4·7 years and was inoculated 30 months before. All monkeys in these two groups developed clinical signs of infection after six to 28 months. Four mangabey monkeys had sitting intraocular pressure (S) of <10 mmHg and seven monkeys had postural change in intraocular pressure (C) of >5; furthermore, four monkeys had postural change in intraocular pressure (C) of >10 in one or both eyes.

Six mangabey monkeys had positive nasal smears for acid fast organisms. Three of these monkeys had a sitting intraocular pressure (S) of <10 mmHg and five had postural change in intraocular pressure (C) of >5. In this group the mean sitting intraocular pressure (S) was 9·75/9·75 mmHg (SD 4·63/6·77), and the mean postural change in intraocular pressure (C) was 5·87/9·00 mmHg (SD 4·28/6·76).

Two mangabey monkeys had conjunctival granulomas (biopsy-positive for acid fast bacilli); all others had eyes of normal appearance.

African green monkeys. The African green monkeys were inoculated between five and 73 months before our examination. One monkey had developed clinical findings 43 months after inoculation. In seven monkeys the intraocular pressure (S) was <10 and the intraocular pressure (C) was >5 in one or both eyes. In the African green monkeys the mean intraocular pressure (S) was 7·25/6·63 mmHg (SD 3·11/3·57), and the mean intraocular pressure (C) was 6·88/8·25 mmHg (SD 2·71/2·91). The eyes of all this group appeared normal, and the nasal smears were negative for acid fast organisms.

Discussion

The discovery of what appears to have been a natural infection with *M leprae* in a mangabey monkey (A015) several years ago has given us the possibility of studying the natural evolution of ocular lepromatous disease. Finding ourselves limited to the observation of low intraocular pressures in many humans with Hansen's disease and without knowing the duration or mode of infection in these patients, we turned to the non-human primate model for further study.[2,3]

Three species of monkeys have now been studied – rhesus, mangabey, and African green. The mangabey is the most susceptible to infection and develops typical clinical disease. All eight that we evaluated developed typical clinical manifestations of Hansen's disease six to 28 months following inoculation. Of this same group five out of eight had significantly low intraocular pressures (S) and seven out of eight had significant postural changes in intraocular pressures (C) of one or both eyes.

The rhesus monkey is moderately susceptible to *M leprae*. In the group that we studied two of eight developed clinical signs of Hansen's disease four to eight months after inoculation. Of this same group five of eight had a signficantly low intraocular pressure and significant postural changes in intraocular pressure.

The African green monkey is the most resistant of the three species to *M leprae*. In the group we studied only one monkey developed clinical manifestations of Hansen's disease, while seven out of eight had significantly low intraocular pressure and significant postural changes in intraocular pressure.

Our data indicate that, regardless of species, susceptibility to the organisms and the development of clinical manifestations of Hansen's disease, there is a significant chance of organismal spread by haematogenous dissemination or by the autonomic nervous system once the subject is inoculated with the organism. Haematogenous spread and/or autonomic spread of the organism results in the organism often becoming localised in the ciliary body region, which in turn causes early damage to the autonomic nerve fibres and end organs.

Low intraocular pressure in disease states results from reduced aqueous humour production or increased uveoscleral outflow. Significant postural change in intraocular pressure is thought to be the result of reduction of local adrenergic receptors in the anterior segment. We believe the damage is manifested in our monkeys by reduction of intraocular pressure and loss of homoeostasis in the intraocular pressure on change in posture.

In humans the damage is manifested by reduction of intraocular pressure, loss of homoeostatic mechanisms for intraocular pressure control, loss of accommodation, pinpoint or irregular pupils, a low-grade iritis, and phthisis bulbi. Pathological examinations of human eyes also show damage to the ciliary body and anterior uveal tract, with atrophy and hyalinisation of the ciliary body.[4-11]

The ocular complications in Hansen's disease are limited to the anterior segment of the eye. The ocular adnexa (brows, lids, eyelashes, and nasolacrimal system), conjunctiva, cornea, sclera, iris, and lens are often involved. These structures are probably favoured sites of localisation and multiplication of the leprosy bacillus because of their relatively cool temperature, their rich nerve supply, and the presence of levodopa (a precursor for melanin pigment).[12-14]

None of the monkeys which we studied have had ocular changes clinically. Repeated examinations of these monkeys, however, will give us a unique opportunity to follow the complex mechanisms of ocular leprosy, and of much interest will be the eventual outcome of the eyes which show decreased intraocular pressures and loss of homoeostatic mechanism of intraocular pressure control.

NH Was supported in part by the E A Baker Foundation, Canadian National Institute for the Blind, Canada, the Aga Khan Foundation, Switzerland; and the Albert and Lotte Haas Foundation, San Francisco.

BJ Gormus was supported in part by grant 2R22AI19302 from the National Institute of Allergy and Infectious Diseases, grant RR=00164 from the National Institute of health, and by a grant from the Victor Heiser Program for Leprosy Research

1 Hussein N, Courtright P, Ostler HB, Hetherington J, Gelber RH. Low intraocular pressure and postural changes in intraocular pressure in Hansen's disease patients *Am J Ophthalmol* 1989; 108: 80–3.
2 Martin LN, Gormus BJ, Wolf RH, Walsh GP, Meyers WM, Binford CH. Experimental leprosy in nonhuman primates *Adv Vet Sci Comp Med* 1983; 28: 201–36.
3 Meyers WM, Walsh GP, Brown HL, *et al* Leprosy in a mangabey monkey – naturally acquired infection *Int J Lepr Other Mycobact Dis* 1985; 53: 1–14
4 Greaves D, Perkins ES. Influence of the sympathetic nervous system on the intraocular pressure and vascular circulation of the eye. *Br J Ophthalmol* 1952, 36: 258–64
5 Jaffe NS. Sympathetic nervous system on the intraocular pressure *Am J Ophthalmol* 1948; 31: 1597
6 Slem G. Clinical studies of ocular leprosy *Am J Ophthalmol* 1971, 71: 431–4
7 Allen JH, Byers JL. The pathology of ocular leprosy I Cornea *Arch Ophthalmol* 1960; 64: 216–20
8 Hashizuma H, Shionuma E. Electron microscopic studies of lepromatous changes in the iris *Int J Lepr Other Mycobact Dis* 1965; 33: 61–82.
9 Pattyn SR. Bacteriology of *Mycobacterium leprae* *Lepr Rev* June 1983 (special issue).
10 Holmes WJ The eyes in leprosy. *Trans Ophthalmol Soc UK* 1961; 81: 397.
11 Holland MGL, Sallman V, Collins EM. A study of the innervation of the chamber angle *Am J Ophthalmol* 1956; 42: 148–61.
12 Ffytche TJ. Role of iris changes as a cause of blindness in lepromatous leprosy *Br J Ophthalmol* 1981, 65. 231–9
13 Spaide R, Nattis R, Lipka A, D'Amico R. Ocular findings in leprosy in United States *Am J Ophthalmol* 1985, 100: 411–6
14 Ffytche TJ. The eye and leprosy (Editorial) *Lepr Rev* 1981, 52: 111–9.

British Journal of Ophthalmology, 1990, 74, 650–653

A survey of the initial referral of children to an ophthalmology department

Wang Yu-dong, J R Thompson, D B Goulstine, A R Rosenthal

Abstract

We report on a survey of the referral of 525 children making their first visit to an ophthalmology department. Information was gathered by interviewing the parents and reviewing the case notes. Parents and relatives initiated the referrals in 223 cases (42%) and health visitors initiated a further 123 cases (23%). General practitioners were rarely the first to notice a condition, though they played a major part in the subsequent referral process. Of 556 reasons for referral squint was the most important (319 cases, 57%), followed by poor vision (106 cases, 19%). There were 44 confirmed cases of amblyopia, of which 15 (34%) were not detected until the child was aged 5 years or over. The overall accuracy of referral was 66% (367 reasons for referral confirmed). In 109 cases (21%) the child was found to be normal. Parents and relatives first noticed 54% of cases of confirmed squint but only 15% of the cases of poor vision. Health professionals, especially health visitors, were of great importance in first detecting poor vision.

Several studies have been conducted on the referral of adults to hospital eye services by general practitioners and ophthalmic opticians.[1-5] However, no studies of the referral of children to an ophthalmology department have been described previously.

The aim of this study was to investigate the process whereby children are referred to the outpatient clinics of an ophthalmology department. In particular we were concerned to evaluate the accuracy of the referral diagnoses and to assess the extent of unnecessary referrals.

Material and methods

The survey started on 1 December 1988 and finished on 31 March 1989. During that time all first time referrals to the outpatient clinics of the eye department of the Royal Infirmary in Leicester, England, were monitored. The Department of Ophthalmology of Leicester Royal Infirmary is the only hospital eye department serving the National Health Service in Leicestershire. The hospital runs peripheral eye clinics in some of the towns in Leicestershire, and therefore the patients seen at the Royal Infirmary were mostly from the City of Leicester and its surrounding suburbs. All children aged under 17 who were referred to the service were included in the survey. Those initially seen in the eye casualty department were not included.

Department of Ophthalmology, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX
W Yu-dong
J R Thompson
D B Goulstine
A R Rosenthal

Correspondence to:
Dr John Thompson.

Accepted for publication
10 April 1990

Table 1 Number of referrals by age and sex

Sex	Age (years)																
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Male	66	37	22	55	16	24	13	18	10	6	1	8	2	5	0	1	2
Female	48	27	16	46	17	21	11	14	10	8	8	5	4	1	3	0	0

Table 2 The ethnic origin of the children from Leicester City

	Referral survey	Council survey
	Leicester City Postcode (n=395)	Leicester City (n=67340)
Caucasian	67%	66%
Asian	30%	30%
Others	3%	4%
Total	100%	100%

For the purposes of this survey an initial visit was defined as the first visit to any ophthalmology department for the suspected condition, and the child's age was taken as at the date of referral.

Data were collected by a single ophthalmologist (WYD) by means of an interview with the parents and the careful reading of case notes and referral letters. Subsequently each child was followed up until a definitive diagnosis was made.

The data collected on each child were date of birth, sex, race, the date when the suspected defect was first noticed, the person who first noticed it, the dates of first contact with health agents prior to referral to the hospital, the date of referral to the hospital, reports of symptoms, reasons and purpose of referral, and the diagnoses and other results of the examination by the child's ophthalmologist or orthoptist.

The accuracy of referral was assessed by comparing the reasons for referral with the final diagnosis. The reasons for referral were considered accurate if the primary diagnosis suggested by the last contacted referring agent was confirmed by the ophthalmologist or orthoptist, or if the symptoms reported corresponded to the final diagnosis.

Results

During the four months of the survey 539

Table 3 The person who first noticed the suspected defect

	Number	Percentage
Parents or relatives	223	42
HV	123	23
PMT	59	11
Child	23	4
School Nurse	22	4
CMO or SMO	21	4
Paediatric Services	20	4
GP	15	3
Others	19	4
Total	525	100

HV=health visitor. PMT=physiological measurement technician. CMO=community medical officer. SMO=school medical officer. GP=general practitioner.

Table 4 Reason for the referral

	Number	*Percentage*
Squint	319	57
Poor vision	106	19
Runny eyes	23	4
Lump on lid	20	4
Epicanthus	10	2
Family history	8	1
Other	70	13
Total	556*	100

*In 31 cases two reasons were given.

children were referred to the hospital clinics, of these 14 were lost to follow-up and thus did not have a final diagnosis. The results below refer to the remaining 525 children.

Table 1 shows the age and sex distribution of the referrals. The mean age at referral was 3·7 years, and 286 (55%) of the cases were male. Males and females were similar in their age distribution. The most frequent attenders were in the groups aged under 1 year and aged 3 years, representing 28% and 19% of the total respectively. These peaks correspond to nine months and 3·5 years' screening. Nearly 70% of children were aged under 5. Those aged 12-16 accounted for only 3%.

The ethnic origins of the children with Leicester City Postcodes are shown in Table 2. A comparison can be made with the estimated breakdown of the population of children aged under 16 produced by the City Council in 1983.[6] The percentages are very similar.

Table 3 shows the person who first noticed the suspected defect that led to the eventual referral. The largest group is parents and relatives, who accounted for 42% (223 cases).

Parents were found to notice defects in younger children. Out of the 213 cases first noticed by parents 180 (85%) were by parents of children aged under 5. When a defect was first noticed by a relative, it was usually by the mother.

The rest of the initiating may be divided into two main groups: the family health care team – health visitor and general practitioner – and school health care team – physiological measurement technician (PMT), school nurse, and school medical officer (SMO). Of the 138 patients first detected by family health carers 130 (94%) were aged under 5. In the 5–11 age group, the school health carers found 54% of cases.

Of the 525 patients referred to the eye department 201 had their first contact with a health visitor. Of these children 54 were aged under 1 year and 69 were aged 3 years, corresponding to the nine months and 3·5 years' screening.

Table 4 lists the reasons for referral. In 31 cases two reasons were given, so that the table shows more reasons than there were children. The reasons for referral were classified by the symptoms, in some cases with anatomical locations. Squint was the most important reason for referral (319 cases, 57%) followed by poor vision (106 cases, 19%).

On average the children had to wait 63 days (range 0 to 289 days) between referral and the outpatient appointment; 480 cases (91%) waited less than three and half months. Only 2% had to wait more than 6 months. There was no difference between city area and county area in waiting time.

The sources of the referrals are summarised in Table 5, 47% of children were finally referred by their general practitioner. Of the remaining cases 24% were referred by a health visitor and 11% by a PMT. 74% of the children were referred after contact with just one agent, and a further 21% were referred after contact with two agents. Three contacts were made by 5% of the children and four contacts by less than 1%. No child had more than four health service contacts prior to referral.

Table 6 shows the diagnoses given at the ophthalmological outpatient consultation. Since 186 cases were given more than one diagnosis, the figures do not correspond to the total number of cases; 109 cases were normal. The most frequent diagnosis was refractive error (hyperopia, myopia, or astigmatism (242, 32%), followed by strabismus, including heterophoria, (216, 29%). Amblyopia accounted for 6% (44 cases). Since the treatment of amblyopia becomes less effective by 5 or 6 years of age and largely ineffective by 9 years of age,[7] the age of detection of each case of amblyopia was determined. Thirty cases (67%) were found before the age of 5 years, 10 cases (23%) were found aged between 5 to 8 years, and four cases (9%) were found aged over 8 years. This indicates that in a number of children the condition had been missed at an earlier screening check. Thirteen (30%) of the cases of amblyopia were due to strabismus, 12 (27%) were due to anisometropia, and 13 (30%) were due to mixed strabismus and anisometropia. In the cases of amblyopia due to strabismus or mixed strabismus and anisometropia 20 (77%) were detected before the age of 5 years, whereas only six (50%) of those due solely to anisometropia were detected by that age.

Table 7 shows the accuracy of referral by

Table 5 Source of the referral

		Contacts in the chain of referral	
	Immediate Source (n=525)	*Percentage of contacts (n=691)**	*Percentage of children (n=525)*
General practitioner	47%	38%	50%
Health visitor	24%	29%	38%
PMT	11%	9%	12%
CMO or SMO	8%	7%	9%
School nurse	3%	3%	5%
Paediatric service	4%	4%	5%
Optician	1%	7%	9%
Other	2%	2%	3%
Total	100%	100%	131%*

*In 136 cases more than one contact was made.

Table 6 Hospital diagnosis

	Number of diagnoses	*Percentage of diagnoses (n=755)***	*Percent of cases (n=525)*
Normal	109	14%	21%
Hyperopia	143	19%	27%
Strabismus	118	16%	22%
Heterophoria	98	13%	19%
Astigmatism	56	7%	11%
Epicanthus	53	7%	10%
Amblyopia	44	6%	8%
Myopia	43	6%	8%
NLD stenosis*	19	3%	4%
Chalazion	14	2%	3%
Conjunctivitus	12	2%	2%
Others	46	6%	9%
Total	755**	100%	144%**

*Nasolacrimal duct stenosis. **In 186 cases more than one diagnosis was given

Table 7 Accuracy of referral categorised by the reason for the referral and the immediate source of the referral: percentages with (totals in parentheses)

	Source of referral							
Reason	*GP*	*Health Visitor*	*PMT*	*CMO or SMO*	*Paediatric service*	*School nurse*	*Others*	*Total*
Squint	64% (137)	42% (89)	63% (51)	68% (31)	75% (4)	100% (1)	80% (6)	58% (319)
Poor vision	85% (41)	58% (27)	100% (10)	80% (10)	0% (1)	100% (13)	100% (4)	80% (106)
Runny eye	91% (22)	–	–	–	100% (1)	–	–	91% (23)
Lump on lid	94% (18)	–	–	100% (1)	100% (1)	–	–	95% (20)
Epicanthus	86% (7)	0% (1)	–	–	100% (1)	–	0% (1)	70% (10)
Family history	0% (2)	40% (5)	–	–	100% (1)	–	–	38% (8)
Other	71% (38)	83% (6)	–	–	56% (15)	0% (1)	60% (1)	67% (70)
Total	72% (265)	46% (128)	69% (61)	71% (42)	63% (24)	93% (15)	71% (21)	66% (556)

referring agents and by the reasons for referral. The overall accuracy of referral was 66% (367 reasons confirmed), for squint it was 58% (185) and for poor vision it was 80% (85). As can be seen from Table 7, the general practitioner was the only agent who referred a large range of eye diseases. The accuracy of referral for poor vision by the PMT (10 cases) and school nurse (13 cases) was 100%, while referral by health visitors for poor vision had 58% accuracy. For squint the accuracy of referral by health visitors was 42%. Only six cases were immediately referred by opticians (Table 5), though 48 contacts were made by opticians in the referral chain. Poor vision and squint were the leading reasons (80%) for referral in this group of patients. When health visitors were the sole referring agent, the accuracy was lowest at the nine months screening. There was a tendency for the accuracy to increase with the child's age.

Table 8 shows the accuracy of referral by the person who first noticed the defect and the reason for referral. Parents and relatives first noticed 240 (43%) of the reasons for subsequent referral and had an overall accuracy of 76%. They first picked up 47% of all suspected squints and 54% of all confirmed squints. However, parents and relatives first noticed only 15% of suspected, and 15% of confirmed, poor vision cases. The largest number of suspected poor vision cases was found by the health visitor.

Discussion

The type and quality of the information in the referral letters varied with the referring agents. In the referring letters by general practitioners there were descriptions of symptoms, primary diagnoses, and in some cases, such as those with conjunctivitis, the treatment and efficiency of the treatment. These cases were referred for advice on treatment including some for surgery. Most of the other referring agents tended to refer cases primarily on their account of symptoms. Opticians were more likely than general practitioners to provide details of an ophthalmic examination and indicate the anatomical location of a problem.

Among the reasons for referral patients with red eyes, lump on lid, and runny eyes were the most likely to be referred correctly. The most important reasons for false positive referral in this study were squint and poor vision. This may be because in such cases the examination requires the co-operation of the children, and that is especially difficult to obtain in the very young. Usually the false diagnosis of strabismus was due to epicanthus and facial asymmetry.

Harrison[1] *et al* in a study of adult referral found similar types of information in the referral letters from general practitioners and opticians, and, as here, found that general practitioners referred nearly half the cases. The referral systems for children in this survey tended to depend more on the family health carers (HV and GP) and school health carers. The reasons for referral of children were quite different from those for adults. In Harrison and colleagues' survey the most important reasons for referral were visual loss and suspected glaucoma.[1] The visual loss proved to be due mainly to organic lesions such as cataract and retinal diseases. In our survey the most important reasons for referral were squint and poor vision, the latter mainly due to refractive error or strabismus. In our survey the accuracy of general practitioners' referral for squint (64% of total 137 reasons) and poor vision (85% of 41) were higher than in Harrison and colleagues' study, where they found 52% (77) and 80% (74) respectively.[1]

Shaw *et al*[2] studied a sample of 1531 cases of amblyopia referred to the Leicester Royal Infirmary and its peripheral clinics. As in this survey, they found that amblyopia due to anisometropia alone was detected at a later age than amblyopia due to strabismus or mixed strabismus and

Table 8 Accuracy of referral categorised by the reason for the referral and the persons who first noticed the defect: percentages with (totals in parentheses)

	Persons who first noticed the defect									
Reason	*Parents, Relatives*	*HV*	*PMT*	*Patient*	*School nurse*	*CMO or SMO*	*Paediatric service*	*GP*	*Others*	*Total*
Squint	66% (150)	36% (80)	62% (47)	100% (5)	50% (4)	64% (14)	75% (4)	50% (10)	100% (5)	58% (319)
Poor vision	81% (16)	71% (41)	100% (12)	80% (5)	94% (17)	60% (5)	50% (2)	100% (1)	86% (7)	80% (106)
Runny eye	94% (18)	100% (1)	–	–	–	–	100% (2)	100% (1)	0% (1)	91% (23)
Lump on lid	100% (17)	–	–	50% (2)	–	100% (1)	–	–	–	95% (20)
Epicanthus	100% (7)	0% (1)	–	0% (1)	–	–	0% (1)	–	–	70% (10)
Family history	40% (5)	33% (3)	–	–	–	–	–		–	38% (8)
Others	81% (27)	71% (7)	–	55% (11)	100% (1)	100% (1)	50% (12)	50% (4)	43% (7)	67% (70)
Total	76% (240)	49% (133)	69% (59)	67% (24)	86% (22)	67% (21)	57% (21)	56% (16)	70% (20)	66% (556)

anisometropia. They considered a number of reasons why this may be so, one of which was the lack of any accompanying sign in the anisometropic cases, so that the parents had difficulty in detecting it. That suggestion is supported by this survey. Although parents first noticed 62% of the amblyopia due to strabismus or mixed strabismus and anisometropia, they first noticed only 17% of the cases due to anisometropia alone.

Although general practitioners finally referred almost half of all children, not many of the conditions were first found by them. Screening and home visits undertaken by health visitors and eye checks at school performed by the PMT and the school nurse were more important in detecting eye defects. The health visitors played a large part with children aged under 5; the PMT and school nurse were more important for children of school age. When parents first noticed a defect, they sometimes did not take any action for several months, and it was not until the health visitor went to their homes that the referral was actually made.

The higher accuracy of referral first noticed by parents and relatives may be due to a number of factors. Firstly, the parents first noticed the more obvious cases, leaving the health workers to detect the rest. Secondly, the parents have much more contact with their children and therefore have the opportunity to observe the abnormality even when it appeared only intermittently, as with intermittent strabismus. Finally, in some families there were other members suffering from similar eye diseases, making the parents more aware of possible eye disease in their children.

Parents and relatives proved to be good at detecting conditions with obvious outward signs, such as squint, running eyes, and lump on the lid. However, they were not so good at noticing poor vision, and it is in this area that the work of the health professionals is especially important.

We thank the consultants of the Leicester Royal Infirmary for their co-operation with this survey. The work was in part supported by the Anne Allerton Fund

1 Harrison RJ, Wild JM, Hobley AJ. Referral patterns to an ophthalmic outpatient clinic by general practitioners and ophthalmic opticians and the role of these professionals in screening for ocular disease. *Br Med J* 1988; 297: 1162–7.
2 McDonnell J. How do general practitioners manage eye disease in the community? *Br J Ophthalmol* 1988; 72: 733–6
3 Brittain GPH, Austin DJ, Kelly SP, A prospective survey to determine sources and diagnosis accuracy of glaucoma referrals *Health Trends* 1988; 20: 43–4
4 Royal College of General Practitioners. Office of Populations Censuses and Surveys and Department of Health and Social Security *Morbidity Statistics From General Practice 1981–82* London: HMSO, 1986: series MB5 no 1.
5 Dart JKG Eye disease at a community health centre. *Br Med J* 1986; 293; 1477–80.
6 Working Group for the Survey of Leicester. *Survey of Leicester 1983: initial report of the survey.* Leicester City Council and Leicestershire County Council, 1985.
7 Harley RD *Pediatric ophthalmology.* 2nd ed. Philadelphia: Saunders, 1983.
8 Shaw DE, Fielder AR, Minshull C, Rosenthal AR. Amblyopia – factors influencing age of presentation. *Lancet* 1988; ii: 207–9.

British Journal of Ophthalmology, 1990, 74, 654–660

Biometry of the crystalline lens in early-onset diabetes

John M Sparrow, Anthony J Bron, Nicholas A Phelps Brown, H A W Neil

Abstract

Lenticular biometry on non-cataractous lenses has been studied by means of Scheimpflug photography and digital image analysis in 153 patients with early-onset insulin-dependent diabetes and 153 non-diabetic controls. Anteroposterior axial lens thickness, cortical thickness, nuclear thickness, anterior and posterior lenticular curvatures, and anterior chamber depth were assessed. Highly significant differences between the lenses of the diabetic subjects and non-diabetic controls were found. After the effect of age had been accounted for within the diabetic subgroup, diabetic duration was found to be a highly significant determinant of lens dimensions, such that age-related dimensional changes for various biometric parameters were accelerated by between 52% and 121% after the onset of diabetes. Because the diabetic duration of the early-onset diabetic subjects studied in this work was accurately known, this report is the first in which a precise assessment of the effect of 'true' diabetic duration on lens biometry has been possible.

The crystalline lens of the eye is the only human organ which undergoes a steady increase in size due to growth throughout the life of the individual.[1–3] Mitosis in the pre-equatorial lenticular epithelium provides a constant supply of new lens fibres, which are added externally to earlier generations of fibres.[4] While accretion of new fibres continues, older generations of fibres compact within the deeper layers of the lens substance.[3 5] Anteroposterior lens growth is proportionally greater than equatorial growth, so the front and back curves of the lens steepen (radii of curvature decrease) with increasing age.[6]

The crystalline lens of the eye is affected by the diabetic state in a number of ways. The anterior clear zone (first zone of discontinuity) has been noted to be enlarged in young diabetics,[7] and lenses of diabetic patients are larger than those of non-diabetics, after the effect of age has been accounted for.[8] Diabetics are in addition at risk for the development of cataractous changes,[9–16] this risk being especially obvious in younger diabetics.[12 13] True juvenile diabetic cataract is fortunately not common and is associated with diabetes which is metabolically severely out of control.[17 18] This type of cataract probably has a specific mechanism, and may occasionally be reversible if the blood sugar concentration is kept normal.[19]

Diabetes therefore affects the lens in a number of important ways. Previous studies have not differentiated between early and late onset diabetes, and the effects of 'true' diabetic duration have therefore not previously been assessed. The present study examines lens biometry in relation to early-onset insulin-dependent diabetics and controls.

Material and methods

SUBJECTS

One hundred and fifty-three diabetic subjects (96 male) were recruited from general diabetic clinics, a paediatric diabetic clinic, ocular diabetic clinics, and from a population survey of diabetics. Eligible subjects had early-onset insulin-dependent diabetes, defined as diabetes requiring insulin treatment from initial diagnosis, with age at onset being 30 years or less. Recruitment was stratified for age and duration of diabetes. An equal number of control subjects were recruited (79 male), mainly from a population based ocular survey, supplemented by subjects from eye hospital clinics and an ophthalmic casualty department. Controls were included if they had no history of diabetes or impaired glucose tolerance, and a non-fasting whole venous blood glucose of less than 7·8 mmol/l.[20 21]

Individual eyes of diabetics and controls were included if the lenses were non-cataractous, had normal anterior ocular segments, and vision sufficiently good for the eye to hold fixation during Scheimpflug photography. Cataractous lenses were excluded because such lenses may have abnormal biometry,[2 22 23] though the following minor opacities as defined by the Oxford clinical cataract classification and grading system[24] were permitted: nuclear brunescence and white nuclear scatter up to and including grade 2, spoke opacities and waterclefts of grade 1, and isolated vacuoles, retrodots, and focal dots. No anterior or posterior subcapsular opacities were permitted, as subcapsular opacities were specifically known to be associated with reduced lens size.[22] There were thus a total of 597 eyes eligible for study in the 306 subjects; 299 were right eyes and 298 were left eyes.

The study was approved by the Central Oxford Research Ethics Committee (ref. no. 1211), and informed consent was obtained from participants.

PROCEDURE

Subjects were recruited to the study by the primary investigator (JS). At the time of their assessments a brief medical history was taken and Snellen visual acuity determined. After the anterior chamber depth had been checked and the presence of iris supported intraocular lens implants excluded, the subject's pupils were

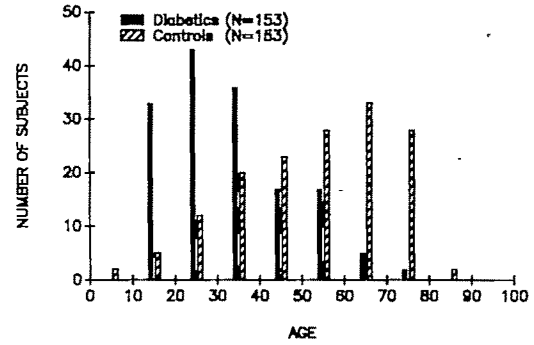
University of Oxford, Nuffield Laboratory of Ophthalmology
J M Sparrow
A J Bron
N A P Brown

Department of Community Medicine and General Practice
H A W Neil

Correspondence to:
Dr John M Sparrow, FRCS,
Department of Ophthalmology, University of Leicester, Leicester Royal Infirmary, Leicester
LE1 5WW.

Accepted for publication
11 April 1990

Figure 1 Frequency distribution of the ages of male and female subjects.



dilated with tropicamide eyedrops 1% and phenylephrine eyedrops 10%, repeated if necessary.

After pupillary dilatation the crystalline lens was examined at a slit-lamp biomicroscope to exclude cataractous changes as described above. Scheimpflug slit-image photography with a Brown Scheimpflug camera[25-27] was then performed, and the photographic images were subjected to digital image analysis by an image analysis system developed by the authors.

Measurements obtained from this system are uncompensated for optical distortions produced by the Scheimpflug camera optics and the corneal and crystalline lenticular magnifications, though separate horizontal and vertical calibration was used for curvature measurements.[28] Anteroposterior biometry (lens thickness, cortical thickness, nuclear thickness, anterior clear zone thickness, and anterior chamber depth) were all measured by a standard method using a linear density trace running down the axis of the Scheimpflug photograph, measurement being facilitated by simultaneous display of both the density trace and the image on adjacent computer screens. Anterior and posterior lens curvatures were measured by defining three points on the curve, the computer program then working out the radius of curvature (calibrated horizontally and vertically).

STATISTICAL METHODS

Biometric measurements were in general obtained from both eyes, though certain patients contributed measurements on only one eye. A preliminary analysis was performed by plotting the biometric data against age and performing simple linear regression of biometry against age for the diabetic and non-diabetic groups. To take account of the within-subject inter-eye correlation, the intra-class correlation model was employed in the analysis.[29-30] All dependent variables were continuous and approximately normally distributed. The analysis took the form of a multiple linear regression analysis with groups (factors), the biometric measures being used as dependent variables in a series of model fitting exercises. Age was therefore treated as a co-variate, compensating for the imperfect age matching of the diabetic and non-diabetic groups where these were being compared.

Significant effects were sought for various patient characteristics. Three series of analyses were performed, the first included all subjects (n=306), the second included only the early onset diabetics (n=153), and the third included only the non-diabetic controls (n=153). Terms were included into the models in a fixed, predetermined order, and this order is adhered to in the summary table of the analysis (Table II). Certain terms were always included in the model (obligatory terms), while others were included only if they were found to be significant at the 5% level (optional terms). Where very powerful effects were found for continuous independent variables (namely, age and duration of diabetes) multiple linear regression slopes for these variables are reported. In this analysis the age slope derived from the control group was imposed on the regression model for the diabetic group, the duration slope therefore being exclusively the additional effect of duration over and above the effect of age. (This method circumvents the statistical problems associated with the fact that age and duration are partially correlated variables.) The analysis was performed by the Generalised Linear Interactive Modelling (GLIM) System of the Numerical Algorithms Group on the Oxford University mainframe computer (VAX cluster).

TABLE 1 *Age by diabetic duration of the early onset diabetes study population*

	Diabetic duration (years)					
Age	*0 to <10*	*10 to <20*	*20 to <30*	*30 to <40*	*40 to <50*	*Total*
0 to <10	0	–	–	–	–	0
10 to <20	22	11	–	–	–	33
20 to <30	20	16	7	–	–	43
30 to <40	5	17	11	3	–	36
40 to <50	–	6	7	3	1	17
50 to <60	–	–	6	6	5	17
60 to <70	–	–	–	4	1	5
70 to <80	–	–	–	–	2	2
Total	47	50	31	16	9	153

0 to <10=up to but excluding 10 years, and so on.

Results

The age distributions of the diabetics and controls are shown in Figure 1, and the age by duration distributions of the diabetics appear in Table 1. Figures 2 to 8 show the results of the preliminary regression analysis of biometry against age. These graphs illustrate that age was an important determinant of the biometry of the anterior ocular segment (an exception to this was the anterior clear zone thickness). Further it can be seen from these graphs that the regression lines for the early onset diabetics differed from those of the non-diabetics. In general the lenses of diabetics appeared larger than those of non-diabetics (Fig 2), this effect being more obvious in the cortex (Fig 3) than in the nucleus (Fig 4). The anterior clear zone of the diabetics was also considerably larger than that of the non-diabetics (Fig 5). The larger diabetic lenses were associated with shallower anterior chambers (Fig 6), and with steeper curvatures (smaller front (Fig 7) and back (Fig 8) radii of curvature).

Formal analysis confirmed these preliminary findings. A summary of p values from the formal analysis appears in Table 2. From the all-subjects analysis (306 subjects) in this table it is apparent that age was a powerful determinant of biometry. These effects were such that older age was associated with larger lens dimensions,

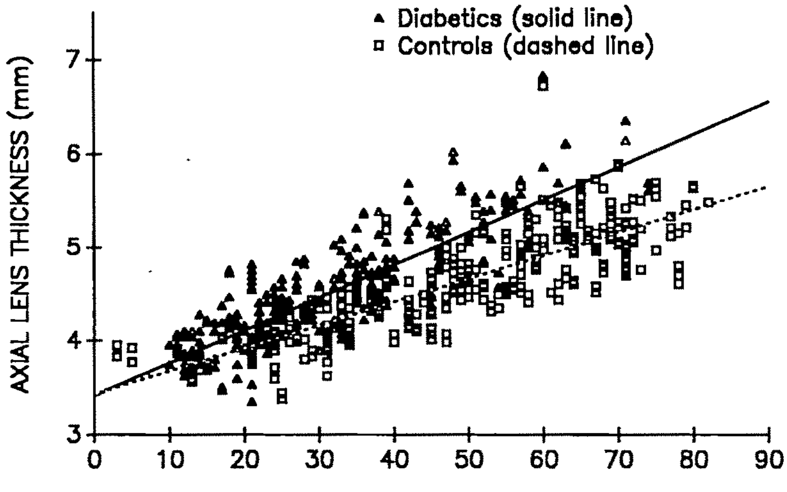


Figure 2 Plot of anteroposterior axial lens thickness in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

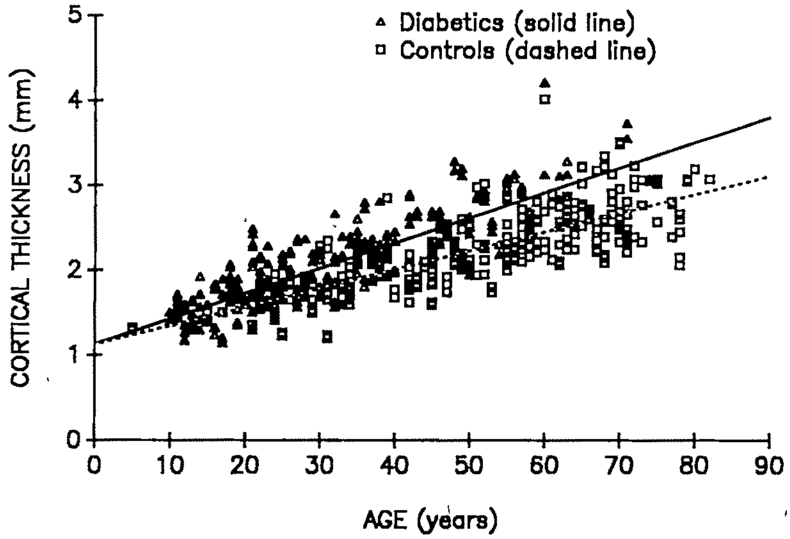


Figure 3 Plot of anteroposterior cortical thickness of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

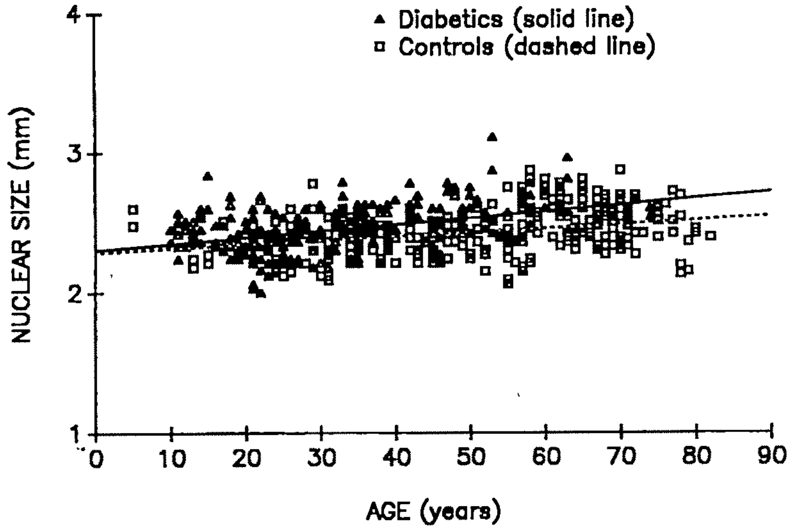


Figure 4 Plot of anteroposterior nuclear size of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

shallower anterior chambers, and steeper surface curvatures. Diabetic status was also a powerful determinant of biometry, with diabetic lenses being larger, being associated with shallower anterior chambers, and having steeper front and back curvatures than those of controls. The significant age by status interactions (Age. Sta) for axial lens thickness, cortical thickness, and anterior chamber depth were such that the slopes of the regression lines against age for the diabetics were significantly steeper than those of the controls (see Figs 2, 3, 5). The effect of sex was such that female sex was associated with decreased cortical thickness, with increased nuclear size, and with decreased anterior chamber depth.

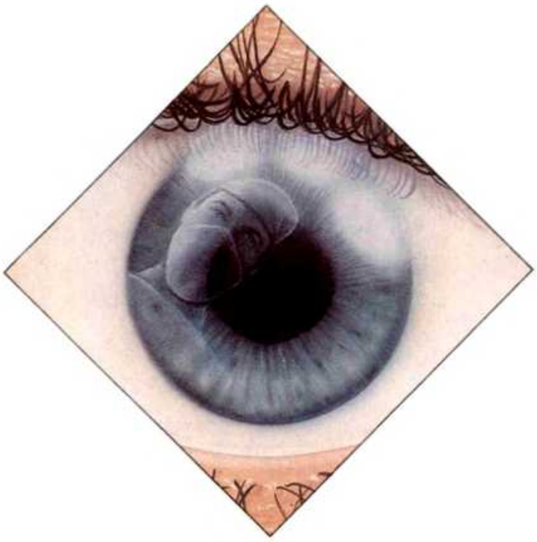
In the early onset diabetes subgroup (153 subjects) age was powerfully associated with biometry. Diabetic duration was generally also a powerful determinant of biometry. Female sex was associated with decreased cortical thickness. Higher daily insulin dose was associated with reduced nuclear size and increased anterior clear zone thickness. The presence of diabetic retinopathy was associated with a larger lens nucleus, with increased anterior clear zone thickness and with steeper surface curvatures.

In the non-diabetic controls subgroup (153 subjects) age was again powerfully associated with biometry. Among the controls female sex was associated with smaller cortical thickness and larger nuclear size.

The linear regression slope for age alone in the non-diabetic controls subgroup, and the multiple linear regression slope for duration in the diabetic subgroup (effect of age fixed to that of the control group), are displayed in Table 3. Also displayed are associated p values from the intraclass correlation analysis, and the duration/age slope ratios. (Anterior clear zone was excluded because age and diabetic duration were not powerful determinants of this feature.) These duration slopes indicate the additional effect of diabetic duration over and above the normal effect of age. For the various biometric parameters in Table 3 the ratio of the slopes of age and duration demonstrate that the independent effect of diabetic duration per year on biometry is between 52% and 121% of the effect of age per year, with the effect on overall lens thickness being 68% and that on anterior chamber depth being 100%.

Discussion

The present work confirms earlier findings that the diabetic state profoundly affects the biometry of the crystalline lens,[7,8] and it has extended this knowledge in terms of the biometry of the anterior ocular segment as a whole in non-cataractous early onset diabetics and non-diabetic controls. In addition other patient characteristics have been examined, and it is clear from the results of this study that duration of diabetes is of paramount importance in the determination of anterior segment biometry in early onset diabetics. The data show that in these diabetics, from the time of diagnosis, the rate of change of lenticular biometry per year increases markedly. Other subject features (sex, daily insulin dose,



...WHEN YOU CHOOSE THE RIGHT SOLUTION

Alcon

BSS®

BALANCED SALT SOLUTION

With most ocular irrigation solutions corneal clouding can begin within a few minutes of commencing surgery. Whilst this clouding is usually reversible, it does make intraocular surgery such as cataract surgery more difficult because the detail within the eye is greatly obscured.[1]

BSS overcomes this problem. It has been designed to be similar to the physiological fluids that naturally bathe the eye. BSS therefore maintains a clear cornea and ensures that you can see the fine detail within the eye throughout surgery.[1,2]

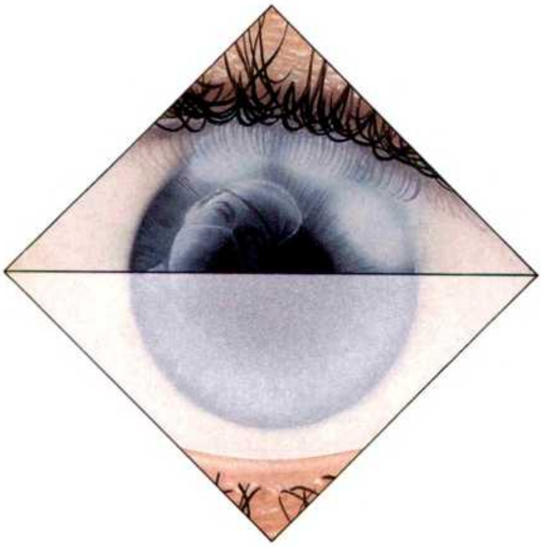
250ML AND 500ML BOTTLES

BSS is now available in a new 250ml size, specifically designed for the longer cataract procedures. One bottle will last through the whole operation and results in less wastage. BSS is now available in a full range of sizes ideal for all your surgical requirements.

So don't let the wrong solution cloud your vision.

Remember – only Alcon Balanced Salt Solution is – BSS.

® Registered Trademark.



THE DIFFERENCE IS CLEAR...

Prescribing Information.

Presentation: A sterile physiological balanced salt solution which is isotonic to the tissues of the eye. Containing Sodium Chloride Ph.Eur. 0.64%, Potassium Chloride Ph.Eur. 0.075%, Calcium Chloride Ph.Eur. 0.048%, Magnesium Chloride Hexahydrate Ph.Eur. 0.03%, Sodium Acetate Ph.Eur. 0.39%, Sodium Citrate Ph.Eur. 0.17% and Water for Injection Ph.Eur.

Uses: As a physiologic irrigating solution.

Dosage and Administration: Sufficient to produce the required irrigation.

Contra-indications, Warnings, etc:

There are no specific contra-indications for this product. When the corneal endothelium is abnormal, irrigation or any trauma may result in bullous keratopathy.

Not for intravenous infusion.

Contains no preservatives and should not be re-used.

Legal Category: P

Package Quantities: 15ml and 30ml Steri-Unit Drop-Tainer dispensers and 250ml and 500ml glass infusion bottles.

Product Licence Number: 15ml and 30ml Steri-Unit Drop-Tainer 0649/0007: 250ml and 500ml glass infusion bottles 0649/0099.

References

1. McDonnell PJ, Spalton DJ, Corneal clarity during extracapsular cataract surgery. Implant & Refractive Surgery, 1987; **6** (1): 9-13.
2. McDermott ML, et al, Ophthalmic Irrigants: A current review and update. Ophthalmic Surgery, 1988; **19** (10): 724-733.

Company Name and Address:

Alcon Laboratories (UK) Ltd,
Imperial Way, Watford,
Herts WD2 4YR.

Alcon

BSS®

BALANCED SALT SOLUTION

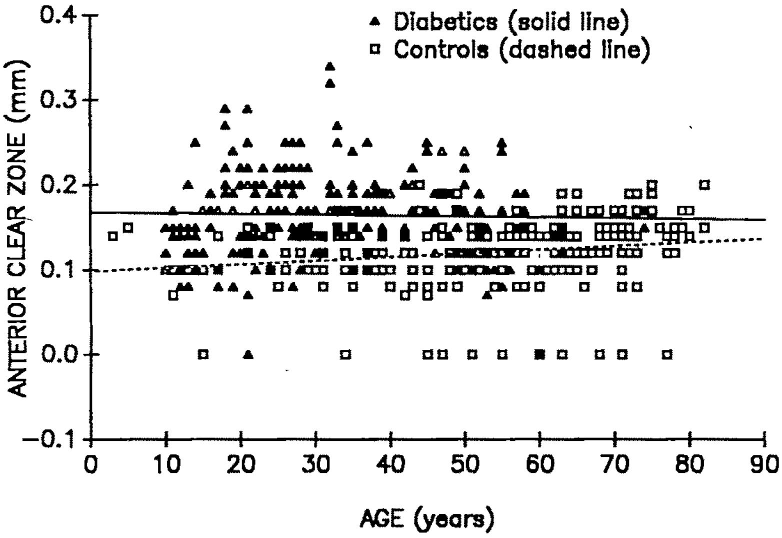


Figure 5 Plot of anterior clear zone thickness of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

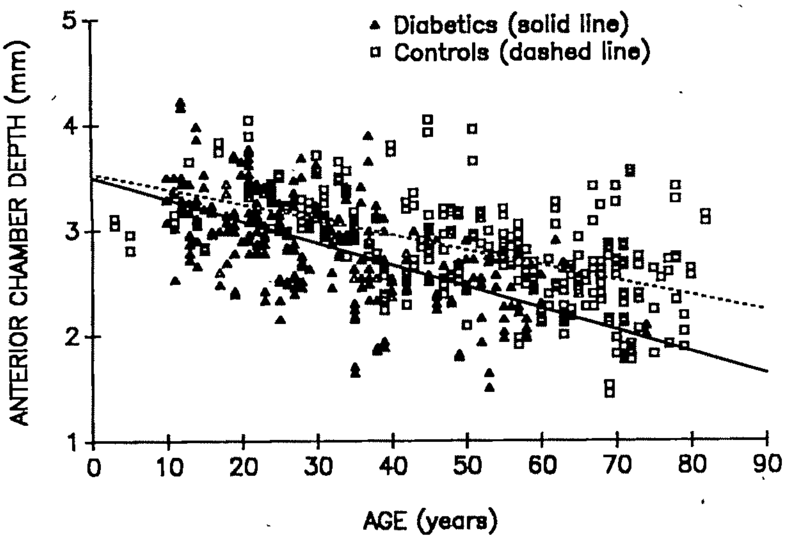


Figure 6 Plot of axial anterior chamber depth of the eye in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

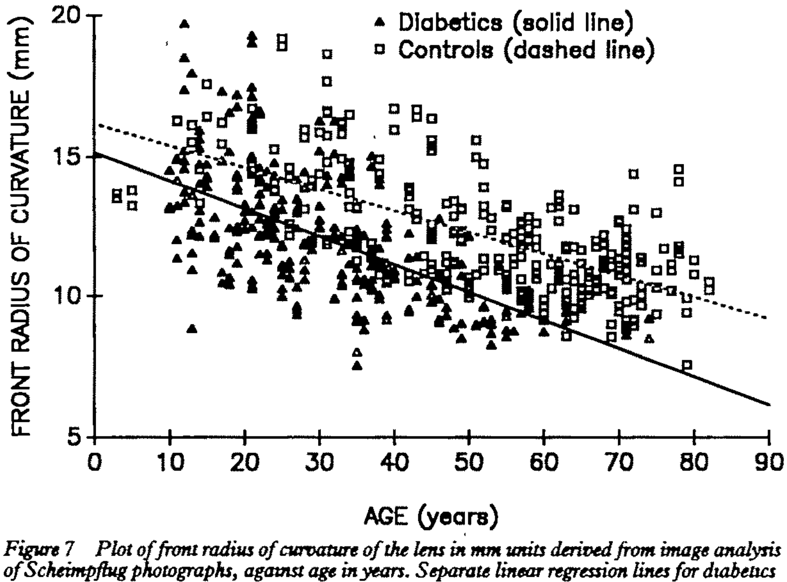


Figure 7 Plot of front radius of curvature of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

and presence of diabetic retinopathy) were of variable importance.

The anterior clear zone is of special interest because it behaves independently of the other zones of the lens. This zone has attracted attention in health[32] and disease[33], being reduced in cataractous lenses[22 23] and increased in lenses of diabetics.[7 8] In the present work the finding of an increased anterior clear zone thickness in diabetes is confirmed, though no relationship with duration has been found. This zone appears to represent a phase in the maturation of young cortical fibres, which sink through it into the deeper cortex as they mature. It has been suggested that the size of this zone reflects the rate of growth of the lens at any particular time.[33] If maturation takes a fixed period, then in a situation of accelerated 'growth' more (or larger) fibres would be in this phase of maturation, and the zone would therefore become wider. The converse would apply in lenses where growth was slowed or halted, when the zone could be expected to shrink or even disappear completely. Brown and Tripathi[22] have shown that the clear zone is reduced or absent in lenses with cataracts, posterior subcapsular cataracts in particular, and further that reduction of the clear zone is associated with a 'small for age' axial lens size. Perkins[23] has corroborated these findings by a simple optical method, and has shown that lenses with early cortical and posterior subcapsular cataracts have reduced overall anteroposterior thickness, and that 60% of early cataracts of all types have a deficient anterior clear zone.

The changes in lens dimensions in diabetes may result from an abnormality in the growth of the lens. From the mechanical point of view three possible explanations exist in relation to altered growth characteristics. The rate of new fibre formation might be increased, with more maturing fibres in the anterior clear zone, and more mature fibres making up the increased bulk of the lens. This 'hyperplastic' model would fit with the findings in the present work, in that the dimensional changes as well as the effect of diabetic duration are natural consequences of such a model. Alternatively the number of new fibres produced might be normal, with individual fibres being increased in size. This 'hypertrophic' model could explain the dimensional changes and duration related effects equally well. The hypertrophic change might be limited to the metabolically active superficial nucleated fibres, which would explain the observed events, with hypertrophic fibres, once enlarged, remaining so. A combination of the above two mechanisms might also exist, and there is evidence that cell size and DNA synthesis can be independently regulated by appropriate combinations of cellular growth factors and growth inhibitors.[34] The third possibility in relation to altered 'lens growth' is a reduction in central compaction of mature lens fibres. There may be some support for this notion in the fact that the ratio of the slopes for the effects of duration and age is the highest for nuclear size (Table 3). This may imply less efficient central fibre packing in diabetes. Brown *et al*[35] could not demonstrate any statistically significant difference in superficial cortical fibre size between diabetics and

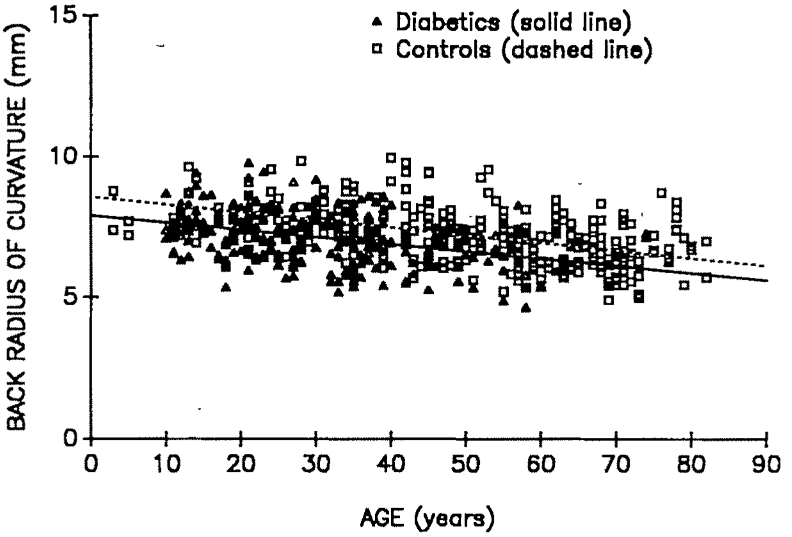


Figure 8 Plot of back radius of curvature of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

non-diabetics, though the numbers of diabetics in this study were small and it is possible that a moderate to small difference may have been missed.

Animal studies have shown that the lenticular epithelium can be stimulated by a number of biological substances. Mitosis can be reinitiated in the epithelium of hypophysectomised frogs by insulin, growth hormone, prolactin and tri-iodothyronine.[36-38] In the rabbit lens insulin, insulin-like growth factors (IGF 1 and 2), and epidermal growth factor (EGF) can stimulate lens epithelial mitosis in serum free culture medium.[39,40] Fibroblast growth factors (basic and acidic FGF) are both mitogenic and capable of inducing changes in cell culture which are characteristic of fibre differentiation in rat lens epithelial explants.[41,42] Several of these growth factors are known to exist in the ocular tissues. Thus eye-derived growth factors (1 and 2) and retina-derived (endothelial cell) growth factors (β and α) are synonymous with fibroblast growth factors (basic and acidic), and angiogenic factor derived from the retina (retina-derived endothelial growth factor) may also be synonymous with a fibroblast growth factor,[42] though this is disputed.[43,44] Lentropin, derived from vitreous humour, has been identified as an insulin-like growth factor which is capable of initiating fibre differentiation in lens epithelial explants from chick embryos.[45] Modulation of the effects of these growth factors by the plasma membrane Na$^+$H$^+$ exchanger (via intracellular pH) may play a part.[46] The above suggests that there are multiple regulatory peptides capable of influencing the mitotic activity of the lenticular epithelium, some of which are structurally similar to insulin, with insulin itself having mitogenic properties. Insulin can also produce a hypertrophic cellular response without stimulation of DNA synthesis.[34].

TABLE 2 *Summary of p values from analysis of lens dimensions in early-onset diabetes and controls (clear lenses)*

	Lens	*Cortex*	*Nucleus*	*ACZ*	*AC*	*FR*	*BK*
All subjects (n=306)							
Age	$\ll 10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$	0·00037	$\ll 10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$
Status	$<10^{-4}$	$<10^{-4}$	0·00002	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$
Age Sta	0 00008	0·0021	NS	NS	0·021	NS	NS
Sex	NS	0·0010	0 00061	NS	0·017	NS	NS
Early-onset diabetes (n=153)							
Age	$\ll 10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$	NS	$\ll 10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$
DUR	$<10^{-4}$	0 000002	0·0049	NS	$<10^{-4}$	$<10^{-4}$	0 00002
Sex	NS	0·0070	NS	NS	NS	NS	NS
INS	NS	NS	0·0057	0·045	NS	NS	NS
BGR	NS	NS	0 045	0·0032	NS	0·047	NS
PLR	NS	NS	NS	0·016	NS	NS	0·034
Controls (n=153)							
Age	$\ll 10^{-4}$	$\ll 10^{-4}$	0·00006	0 010	$<10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$
Sex	NS	0 011	0·0012	NS	NS	NS	NS

AC=anterior chamber depth ACZ=anterior clear zone thickness of lens. FR=front radius of curvature of lens. BK=back radius of curvature of lens STA=diabetic or non-diabetic status. DUR=diabetic duration. INS=daily insulin dose BGR=background retinopathy PLR=proliferative retinopathy

TABLE 3 *Summary of slopes for age and diabetic duration from multiple linear regression analysis of lens dimensions in early-onset diabetes and controls (clear lenses)*

	Lens	*Cortex*	*Nucleus*	*AC*	*FR*	*BK*
Controls (n=153)						
Age slope	+0 025	+0 022	+0·0029	−0·014	−0·077	−0 027
p	$\ll 10^{-4}$	$\ll 10^{-4}$	0 00006	$<10^{-4}$	$\ll 10^{-4}$	$<10^{-4}$
Early-onset diabetes (n=153)						
DUR Slope	+0 017	+0·013	+0·0035	−0·014	−0·068	−0 014
p	$<10^{-4}$	0 000002	0·0049	$<10^{-4}$	$<10^{-4}$	0·00002
Slope ratio (DUR/age)	0 68	0·59	1·21	1·02	0·88	0·52

p=Probability DUR=diabetic duration AC=anterior chamber depth FR=front radius of curvature of lens. BK=back radius of curvature of lens. The slopes for age from the control groups were imposed upon the diabetic groups in order to avoid unwanted distortion of the age and duration slopes due to the effects of partially correlated variables.

There is general agreement that growth hormone (GH) is raised in human diabetes.[47] No consensus exists with regard to IGF 1, however, with levels having been reported which are raised, normal, or reduced in diabetics compared with controls.[48] Raised IGF 1 has been associated with the existence of retinopathy,[49] though this association was not found when an adjustment for the presence of proteinuria was made.[48] In the present work an association between retinopathy and increased anterior clear zone thickness, nuclear size, and steeper curvatures was found (renal status not accounted for). A retina-derived growth factor (which may be raised in eyes with retinopathy) may play a part in this association. Recent work indicates that non-diabetic renal transplant patients have increased anteroposterior lens thickness.[50]

The increased size of the anterior clear zone of the lens in early-onset diabetes is associated in the present study with increased daily insulin dose. Insulin is known to have a mitogenic effect on the lenticular epithelium,[39,40] and it can also induce hypertrophy in an epithelial tissue.[34] The possibility exists that the above association could be significant in terms of a causal role for insulin in stimulating lens growth. In individual diabetic patients the insulin dose would vary from time to time, so the prevailing dose at the time of lens photography may not represent a composite statement about insulin dose covering the entire duration of the diabetic state. On the other hand the prevailing insulin dose may be more relevant to the thickness of the anterior clear zone. Too high insulin dosage or high pulses of insulin associated with insulin injections may be relevant in this regard.[51] From the present data there is no way of distinguishing between changes resultant on the effects of 'worse diabetes' (requiring more insulin), and the possible effects of the insulin itself. The association between increased daily insulin dose and increased nuclear thickness is difficult to interpret.

Extracellular overhydration of the lens as a whole (unless progressive with years of diabetes) cannot easily explain the powerful effect of duration found in the present study. Simple osmotic events related to the polyol pathway[52,53] therefore seem an unlikely explanation. Overhydration at the cellular level, however, remains a possible cause of the biometric changes. Cellular overhydration of metabolically active recently formed fibres only would fit with the 'hypertrophic model', and could satisfactorily explain a duration effect. A number of mechanisms are available by which cellular overhydration could come about. Abnormally functioning membrane pumps might be involved, with damage to Na$^+$K$^+$ ATPase by non-enzymatic glycosylation[54] or oxidation[55] possibly playing a role. (Diabetics may be at increased risk of damage by oxidation from autooxidation of monosaccharides[56,57] or depletion of glutathione.[58,59]) Other membrane pumps could be similarly damaged in the diabetic. Thus, not only NA$^+$K$^+$ ATPase but also Ca^{++} ATPase and the Na$^+$H$^+$ exchanger might be affected. Malfunction of Na$^+$K$^+$ ATPase and the Na$^+$H$^+$ exchanger could affect cellular hydration and fibre size in keeping with the 'hypertrophic model,' while malfunction of the Na$^+$H$^+$ exchanger could also have an effect (by modulation of growth factors) on the mitotic activity of the epithelium.[46,60] The present data do not allow a distinction to be drawn between an abnormality of lens growth and an abnormality of cellular hydration.

The authors are grateful to Dr D Hockaday, Dr J Mann, Dr D Dunger, Mr H Cheng, Mr P Awdry, and Mr A Freedman for allowing their patients to be recruited to this study, and to Dr J Bithell for his statistical advice. This work was supported by Oxford Regional Health Authority NHS Locally Organised Research Grant Number 85/19 and by a British Diabetic Association Research Grant.

1 Weale RA. *The aging eye*. London: Lewis, 1963

2 Weekers R, Delmarcelle Y, Luyckx-bacus J, *et al*. Morphological changes of the lens with age and cataract In Elliot K, Fitzsimons DW, eds. *The human lens in relation to cataract* CIBA foundation symposium 19:1973.

3 Brown NAP. Dating the onset of cataract *Trans Ophthalmol Soc UK* 1976; **96**: 18–23.

4 Marshall J, Beaconsfield M, Rothery S. The anatomy and development of the human lens and zonules. *Trans Ophthalmol Soc UK* 1982; **102**: 423–40.

5 Brown NAP, Sparrow J, Bron AJ Central compaction in the process of lens growth as indicated by lamellar cataract. *Br J Ophthalmology* 1988; **72**: 538–44

6 Brown NAP. The change in lens curvature with age. *Exp Eye Res* 1974; **19**: 175–83.

7 Huggert A The appearance of the band of disjunction of the lens in diabetes mellitus *Acta Ophthalmol (Kbh)* 1953; **31**: 227–34.

8 Brown NAP, Hungerford J The influence of the size of the lens in ocular disease. *Trans Ophthalmol Soc UK* 1982; **102**: 359–63.

9 Caird FI, Hutchinson M, Pirie A Cataract and diabetes. *Br Med J* 1964; **ii**: 665–8.

10 Hiller R, Kahn HA. Senile cataract extraction and diabetes. *Br J Ophthalmol* 1976; **60**: 283–6.

11 Norn MS. Diabetes mellitus and cataracta senilis. *Acta Ophthalmol (KGh)* 1967; **45**: 322–32

12 Ederer F, Hiller R, Taylor HR. Senile lens changes and diabetes in two population studies. *Am J Ophthalmol* 1981; **91**: 381–95.

13 Bernth-Petersen P, Bach E. Epidemiologic aspects of cataract surgery. (3) Frequencies of diabetes and glaucoma in a cataract population. *Acta Ophthalmol (Kbh)* 1983; **61**: 406–16.

14 Schwab IR, Dawson CR, Hoshiwara I, Szuter CF, Knowler WC. Incidence of cataract extraction in Pima Indians diabetes as a risk factor *Arch Ophthalmol* 1985; **103**: 208–12.

15 Eckerskorn U, Hockwin O, Muller-Breitenkamp R, Chen TT, Knowles W, Dobbs RE Evaluation of cataract related risk factors using detailed classification systems and multivariate statistical methods. *Dev Ophthalmol* 1987; **15**: 82–91

16 van Heyningen R, Harding JJ. A case-control study of cataract in Oxfordshire: some risk factors *Br J Ophthalmol* 1988; **72**: 804–8

17 Caird FI, Pirie A, Ramsell TG *Diabetes and the eye* Oxford and Edinburgh. Blackwell, 1969

18 Vinding T, Nielsen NV. Two cases of acutely developed cataract in diabetes mellitus *Acta Ophthalmol (Kbh)* 1984, **62**: 373–7.

19 Brown CA, Burman D Transient cataracts in a diabetic child with hyperosmolar coma. *Br J Ophthalmol* 1973, **57**· 429–33

20 Jarrett JR *Diabetes mellitus*. (Series in clinical epidemiology) London, Sidney Croom Helm, 1986.

21 WHO Study Group. *Diabetes mellitus WHO Techn Rep Ser* 727. Geneva: WHO, 1985.

22 Brown NAP, Tripathi R. The loss of the anterior clear zone of the lens: prognostic significance in cataract formation. *Trans Ophthalmol Soc UK* 1974; **94**: 29–45

23 Perkins ES. Lens Thickness in early cataract. *Br J Ophthalmol* 1988; **72**: 348–53

24 Sparrow JM, Bron AJ, Brown NAP, Ayliffe W, Hill AR The Oxford clinical cataract classification and grading system. *Int Ophthalmol* 1986; **9**: 207–25.

25 Brown NAP Slit-image photography *Trans Ophthalmol Soc UK* 1969; **89**: 397–408.

26 Brown NAP. An advanced slit image camera. *Br J Ophthalmol* 1972; **56**: 624–31.

27 Brown NAP. Quantitative slit-image photography of the lens. *Trans Ophthalmol Soc UK* 1972; **92**: 303–17

28 Sparrow JM. *The lens in diabetes*. D Phil Thesis Linacre College, University of Oxford: 1988

29 Rosner B Statistical methods in ophthalmology: an adjustment for the intraclass correlation between eyes *Biometrics* 1982; **38**: 105–14.

30 Ray WA, O'Day DM, Head WS, Robinson R Statistical analysis for experimental models of ocular disease continuous response measures *Curr Eye Res* 1985, **4**:585–97

31 Ray WA, O'Day DM Statistical analysis of multi-eye data in ophthalmic research *Invest Ophthalmol Vis Sci* 1985; **26**: 1186–8.

32 Goldmann H. Senile changes of the lens and vitreous *Am J Ophthalmol* 1964; **57**: 1–13.

33 Niesel P Visible changes of the lens with age *Trans Ophthalmol Soc UK* 1982; **102**: 327–30

34 Fine L. The biology of renal hypertrophy. *Kidney Int* 1986, **29** 619–34

35 Brown NAP, Bron AJ, Sparrow JM. An estimate of the size and shape of the human lens fibre in vivo. *Br J Ophthalmol* 1987; **71**: 916–22

36 Reddan JR, Harding CV, Rothstein H, Crotty MW, Lee P, Freeman N Stimulation of mitosis in the vertebrate lens in the presence of insulin. *Ophthalmic Res* 1972, **3**: 65–81

37 Wainwright N, Hayden J, Rothstein H. Total disappearance of cell proliferation in the lens of a hypophysectomized animal. *Cytobios* 1978; **23**: 79–92.

38 Rothstein H, Van Wyk JJ, Hayden JH, Weinsider A, Somatomedin C Somatomedin C Restoration in vivo of cycle traverse in G0/G1 Blocked cells of hypophysectomized animals *Science* 1980; **208**: 410–2

39 Reddan JR, Dziedzic DC. Insulin-like growth factors, IGF–1, IGF–2 and somatomedin C trigger cell proliferation in mammalian epithelial cells cultured in a serum-free medium. *Exp Cell Res* 1982; **142**: 293–300.

40 Reddan JR, Wilson-Dziedzic D Insulin growth factor and epidermal growth factor trigger mitosis in lenses cultured in a serum-free medium *Invest Ophthalmol Vis Sci* 1983; **24**: 409–16

41 McAvoy JW, Fernon VTP. Neural retinas promote cell division and fibre differentiation in lens epithelial explants *Curr Eye Res* 1984; **3**: 827–34.

42 Chamberlain CG, McAvoy JW. Evidence that fibroblast growth factor promotes lens fibre differentiation *Curr Eye Res* 1987, **6**: 1165–8.

43 Elstow SF, Schor AM, Weiss JB Bovine retinal angiogenesis factor is a small molecule (molecular mass <600). *Invest Ophthalmol Vis Sci* 1985; **26**: 74–9

44 Taylor CM, Weiss JB, Kissun RD, Garner A. Effect of oxygen tension on the quantities of procollagenase-activating angiogenic factor present in the developing kitten retina *Br J Ophthalmol* 1986; **70**: 162–5.

45 Beebe DC, Silver MH, Belcher KS, van Wyk JJ, Svoboda ME. Lentropin, a protein that controls lens fibre formation, is related functionally and immunologically to the insulin like growth factors. *Proc Natl Acad Sci USA* 1986, **84**: 2327–31.

46 Mahnensmith RL, Aronson PS. The plasma membrane sodium-hydrogen exchanger and its role in physiological and pathophysiological processes. *Circulation Res* 1985; **56**: 773–88

47 Holly JMP, Amiel SA, Sandhu RR, Rees LH, Wass JA. The role of growth hormone in diabetes mellitus *J Endocrinol* 1988; **118**: 353–64.

48 Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM Serum IGF–1 concentration in diabetic retinopathy. *Diabetic Medicine* 1988; **5**: 356–60.

49 Merimee TJ, Zapf J, Froesch ER Insulin like growth factors Studies in diabetics with and without retinopathy. *N Engl J Med* 1983; **309**: 527–30

50 Shun-Shin GA, Bron AJ, Ratcliffe P, Sparrow JM, Brown NAP The lens in renal transplantation *Br J Ophthalmol* 1990; **74**: 267–71.

51 Rizza RA, Gerich JE, Haymond M, *et al*. Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional insulin therapy. *N Engl J Med* 1980; 303: 1313–8.

52 van Heyningen R. Formation of polyols by the lens of the rat with sugar cataracts. *Nature* 1959; 164: 194–5.

53 Kinoshita JH. Mechanisms initiating cataract formation. *Invest Ophthalmol Vis Sci* 1974; 13: 713–24.

54 Garner MH, Spector A. ATP hydrolysis kinetics in Na, K–ATPase in cataract *Exp Eye Res* 1986; 42: 339–48

55 Spector A. Oxidation and cataract. In: Nugent J, Whelan J, eds. *Human cataract formation*. CIBA foundation symposium 106. 1984: 48–64

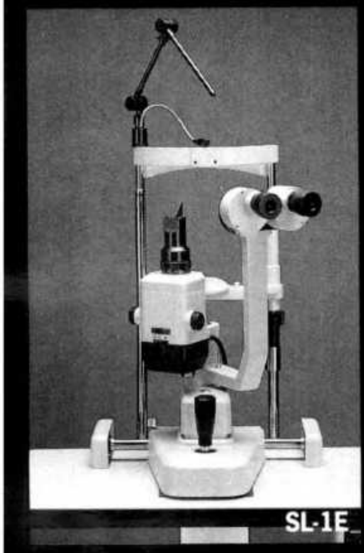
56 Crabbe JC Discussion: Diabetic and galactosaemic cataracts. In· Nugent J, Whelan J, eds. *Human cataract formation*. CIBA foundation symposium 106: 1984: 123–31.

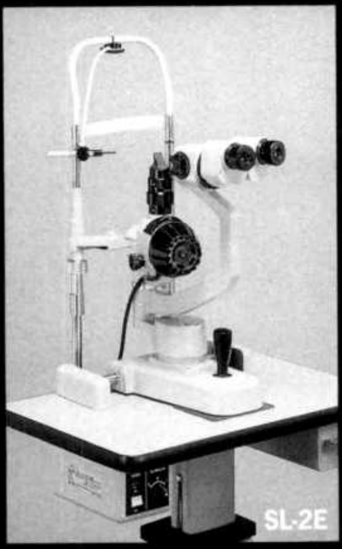
57 Wolff SP, Crabbe MJ. Low apparent aldose reductase activity produced by monosaccharide autoxidation. *Biochem J* 1985; 226: 625–30.

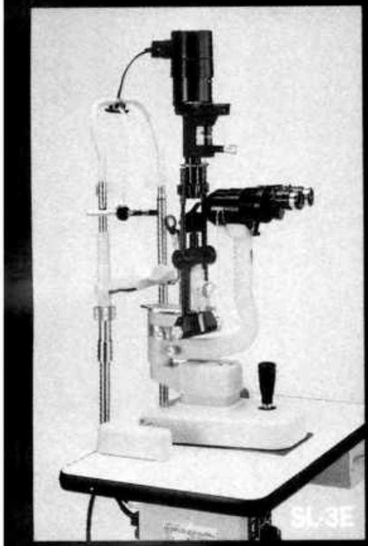
58 Varma SD, Richards RD Etiology of cataracts in diabetics. *Int Ophthalmol Clin* 1984; 24: 93–110.

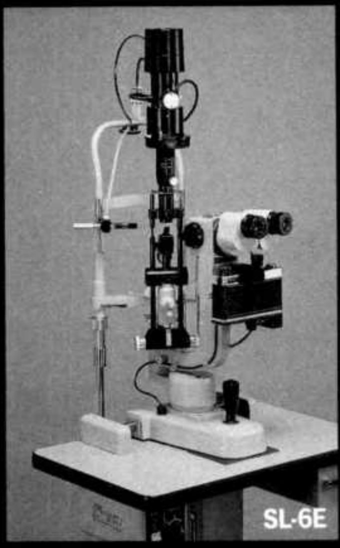
59 Kador PF, Kinoshita JH. Diabetic and galactosaemic cataracts. In: Nugent J, Whelan J, eds. *Human cataract formation*. CIBA foundation symposium 106: 1984: 110–23.

60 Duncan G. Role of membranes in controlling ion and water movements in the lens. In: Elliot K, Fitzsimons DW, eds. *The human lens in relation to cataract*. CIBA foundation symposium 19 1973: 99–116









SL-1E

- 14mm slit illumination
- Omni directional joystick
- Variable magnification capability
- Built-in filters
- Halogen illumination

SL-2E

- Convergent binocular tubes enhance the examination
- Omni directional joystick
- Three-position magnification
- Infinitely adjustable slit width and length
- Built-in filters
- 35mm photographic attachment

SL-3E

- Omni directional joystick
- Two fixation targets
- Convenient, lever-controlled magnification change
- Slit beam inclination
- Four built-in filters
- Infinitely adjustable slit width and length
- Pachometer attachment

SL-6E

- Convergent binocular tubes for unprecedented viewing
- Omni directional joystick
- Five-position magnification
- Four built-in filters
- 35mm photographic attachments
- Polaroid attachment model PA-8S
- Video attachment
- Non-contact specular attachment
- Pachometer attachment
- Observation tube

In keeping with our philosophy of supplying only top quality equipment, Keeler are now the exclusive distributors for TOPCON.

The full range of Topcon slit lamps allows the practitioner to choose exactly the right instrument for his particular needs.

Within the range, Topcon now offers high magnification versions of their most popular slit lamps. These are illustrated opposite, and the details listed below.

If a permanent record is required, then this is achievable with photographic attachments which allow the use of 35mm, Polaroid or, in the case of the SL-6E, video recording.

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

LONDON CENTRE
Keeler Martin and Tomkins, 38 Margaret Street,
Cavendish Square, London W1A 4NS
Telephone: 01-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
Telephone: (0236) 721214 Fax: (0236) 721231

PRESCRIBING INFORMATION

PRESENTATION

clear colourless solution in a plastic dropper bottle. ilauline is available in two strengths containing 0.1% r 0.3% w/v metipranolol together with benzalkonium hloride 0.01% w/v as a preservative.

USES

ilauline is a beta adrenoceptor blocking agent used in ne topical treatment of chronic open-angle glaucoma nd other conditions in which intra-ocular pressure is levated above normal levels.

DOSAGE AND ADMINISTRATION

dults and the elderly: The recommended dosage is one rop instilled into the affected eye(s) twice daily.

hildren: Not Recomended.

lewly diagnosed patients with ocular hypertension or hronic open-angle glaucoma should be treated with ilauline 0.1%, changing to the higher strength if dequate control of intra-ocular pressure is not achieved r maintained. Patients on existing therapy, whether or ot this is to be continued, should receive Glauline 0.3%.

CONTRAINDICATIONS, WARNINGS, ETC

ontraindications: Bronchial asthma, history of ronchial asthma, chronic obstructive airways disease, inus bradycardia, second or third degree trio-ventricular block, cardiac failure, cardiogenic hock, hypersensitivity to any of the components of the reparation.

recautions and Warnings: As with other topically pplied beta-blockers, systemic absorption may occur iving adverse reactions similar to those of orally dministered beta-blockers. Cardiac and respiratory actions have been reported with topically applied eta-blockers including, rarely, death due to ronchospasm or cardiac failure. Congestive cardiac ilure should be adequately controlled before starting erapy with Glauline. If the patient has a history of ardiac disease, pulse rate should be monitored. iabetic control should be monitored during Glauline erapy in patients with labile diabetes. There have been ports of granulomatous anterior uveitis occuring in atients using Glauline. In any case, where a patient hows symptoms or signs suggestive of anterior uveitis, lauline should be withdrawn and an alternative ocular ypotensive agent substituted. Glauline contains enzalkonium chloride as a preservative and should erefore not be used in patients continuing to wear soft ydrophilic) contact lenses. Use in pregnancy: lthough there is no evidence to suggest that etipranolol has teratogenic properties, its use during regnancy should be avoided unless the potential enefits are considered to outweigh the possible hazards.

se in lactation: As beta-blockers can pass into breast ilk, consideration should be given to stopping east-feeding if therapy with Glauline is considered ecessary.

de-effects:

Ocular: Transient burning or stinging on instillation, lurred vision, superficial punctate keratitis, epharoconjunctivitis and anterior uveitis have been ported.

Cardiovascular: Bradycardia and hypotension can ccasionally occur following the systemic absorption of pically applied beta-blockers.

Respiratory: Bronchospasm can occur, edominantly in patients with a history of reversible bstructive airways disease. Dyspnoea and respiratory ilure have also been reported with topically applied ta-blockers.

CNS: Headache, ataxia, weakness and lethargy can ccur.

Dermatological: Local manifestations of contact nsitivity reactions around the eyes can involve skin shes on the lower lids and cheeks, and peri-orbital dema.

rug interactions: Caution should be exercised if used conjunction with oral beta-blockers as additive effects systemic beta blockade may occur. Overdosage: verdosage is unlikely by the ocular route. If excess ug is accidentally administered to the eye, the affected e(s) should be immediately flushed with water or line. If accidental or deliberate systemic ingestion has ken place, bronchospasm, bradycardia, hypotension d cardiac failure may result, and treatment for erdosage of a beta-receptor blocking agent should be itiated.

PHARMACEUTICAL PRECAUTIONS

lauline should not be diluted or dispensed from any ntainer other than the original bottle. The unopened oduct has a shelf life of 3 years, but as with other eye ops the contents of each bottle should be discarded one onth after opening.

EGAL CATEGORY POM

ACKAGE QUANTITIES

auline is supplied as a sterile ophthalmic solution in a nl plastic dropper bottle.

URTHER INFORMATION

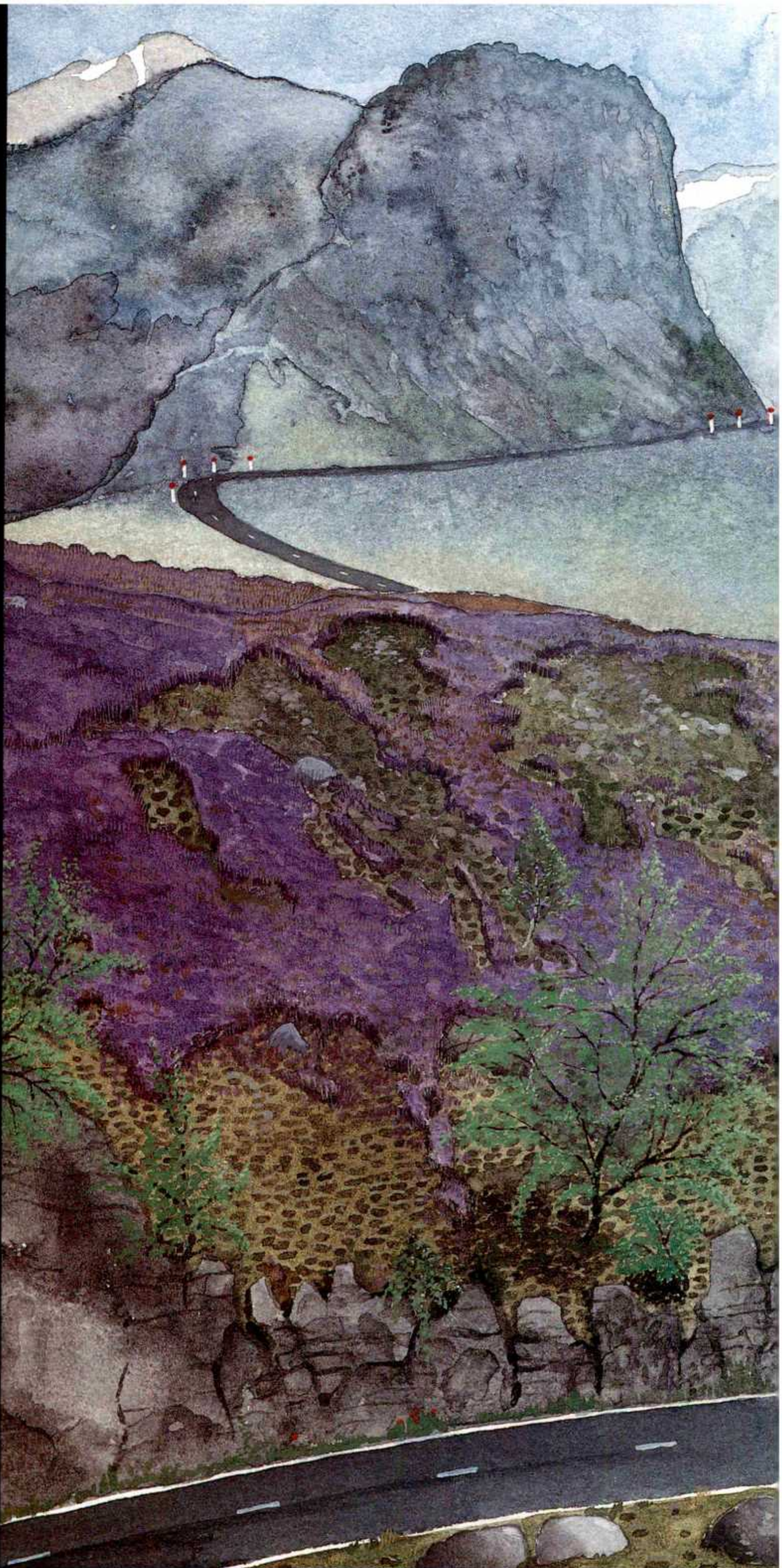
auline reduces intra-ocular pressure with little or no fect on pupil size or accommodation. For newly agnosed glaucoma patients, clinical trial experience ggests that approximately 85% will achieve adequate ntrol of their intra-ocular pressure with Glauline 0.1%.

RODUCT LICENCE NUMBERS

auline 0.1% 0033/0104
auline 0.3% 0033/0105

ASIC NHS PRICE

l. 0.1% £4.93 0.3% £4.67



Glauline

METIPRANOLOL

*Trade Mark

Take the low road

Smith & Nephew Pharmaceuticals Ltd

Bampton Road, Harold Hill,
Romford, Essex RM3 8SL, England
Telephone: Ingrebourne (04023) 4933
Telex: 898 058 SMINEPG
Fax: 04023 71316

Smith+Nephew

Fucithalmic

fusidic acid

Contain
Fucidin
fusidic acid

twice daily for bacterial conjunctivitis

▼ Prescribing Information.
Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses:** Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications:** Bacterial conjunctivitis due to sensitive organisms. **Dosage:** One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications:** Hypersensitivity to any component. **Precautions:** Should not be used when contact lenses are being worn. **Side effects:** Transient stinging. Hypersensitivity may occur. **Product Licence Number:** 0043/0137. **Basic N.H.S. Price:** £2.25/5g tube.

L E O

Further information available on request:

Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

British Journal of Ophthalmology, 1990, 74, 661–662

Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract

Nurettin Akyol, Orhan Değer, E Edip Keha, Saim Kiliç

Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
Department of Ophthalmology
N Akyol
S Kiliç

Department of Biochemisty
O Değer
E E Keha

Correspondence to Nurettin Akyol, Assistant Professor, Department of Ophthalmology Faculty of Medicine, Karadeniz Technical University, 61080 Trabzon, Turkey

Accepted for publication 17 May 1990

Abstract

Serum and aqueous humour zinc and copper concentrations of 44 patients with glaucoma and cataract were determined. Serum values were found within normal ranges. The highest mean copper concentration was seen in the glaucoma group. In addition there was a significant negative correlation between the aqueous humour levels of zinc and copper in patients with glaucoma. It was concluded that an increased copper value together with a low zinc value might be of importance in patients with glaucoma.

Zinc and copper are essential trace elements and are present in ocular tissues.[1] That zinc and copper are needed for the growth and well-being of both plants and animals is well established. The metabolic functions of these elements are largely based on their presence in metalloenzymes.[2] Trace element investigations in the aqueous humour have been carried out in animals.[3 4]

In this study we aimed to determine the aqueous humour zinc and copper levels of patients with cataract and glaucoma and to look for any correlation between these values.

Materials and methods

The study included 44 patients – 20 with senile cataract, 10 with glaucoma, 8 with glaucoma+cataract, and 6 with congenital cataract.

Sterile disposable syringes and hypodermic needles were used to collect blood and aqueous humour samples. The aqueous humour sample was taken during the operation after incision of the conjunctiva and just before opening the anterior chamber. Blood was centrifuged to obtain serum. All samples were immediately stored at −20°C until analysed. All measurements were made with the GBC Scientific Equipment atomic absorption spectrophotometer (Model 902), with copper and zinc hollow cathode lamps at 0·5 slit width and graphite furnace.

The results were analysed by Kruskal-Wallis variance analysis, unpaired *t* test, and correlation analysis.

Results

The results obtained for human aqueous humour zinc and copper concentrations are given in Table 1. Distribution diagrams are given in Figures 1 and 2.

The mean serum zinc concentrations in all groups were within the normal range of our laboratory (0·8–1·4 μg/ml (12·2–21·4 μmol/l)), whereas copper concentrations were slightly higher (0·9–1·60 μg/ml (14–25 μmol/l)). But no significant difference was found among the groups for both zinc and copper. The highest mean aqueous humour copper concentration was found in the group of glaucoma patients. By analysis of variance a significant difference was found among the groups ($p<0·05$) for aqueous humour copper concentrations, but not for zinc. The difference was observed only between the mean aqueous humour concentrations of patients with glaucoma or senile cataract. In addition, correlations were established for aqueous humour, but not serum, between zinc and copper (in the group of glaucoma patients $r=-0·755$, $p<0·01$ and in the group of patients with glaucoma+cataract $r=-0·806$, $p<0·01$) (Fig 3).

Discussion

We could not find any reports on the trace element concentrations in aqueous humour of patients with cataract and glaucoma. Gerhard *et al*[5] found the zinc concentrations as 0·27–0·44 μg/ml (4·1–6·7 μmol/l). Moster *et al*[6] found

Table 1 Zinc and copper concentrations (arithmetic mean and standard error of mean)

		Zinc, mean (SEM) (μg/ml)		*Copper, mean (SEM) (μg/ml)*	
Group	*n*	*Aqueous humour*	*Serum*	*Aqueous humour*	*Serum*
I Senile cataract	20	0·144 (0·010)	1·37 (0·071)	0·047 (0·006)	1·85 (0·154)
II. Glaucoma	10	0·154 (0·020)	1·26 (0·126)	0·112 (0·024)*	1·94 (0·183)
III Glaucoma+cataract	8	0·122 (0·018)	1·42 (0·099)	0·068 (0·015)	1·78 (0·247)
IV Congenital cataract	6	0·178 (0·042)	1·22 (0·098)	0·070 (0·028)	1·80 (0·289)

*Significantly different from group I at $p<0·05$
SI conversion: Zinc μg/ml × 15·3 = μmol/l Copper μg/ml × 15·7 = μmol/l

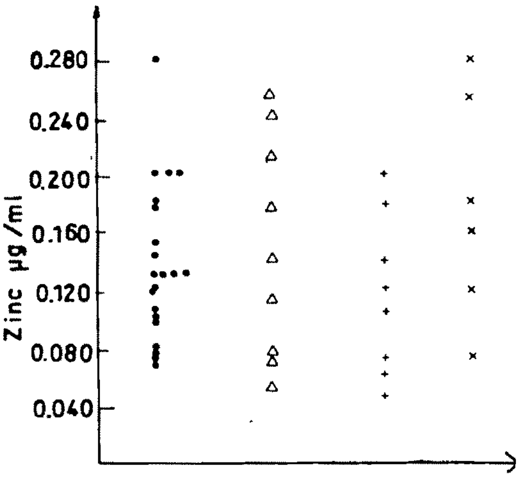


Figure 1 Distribution diagram for aqueous humour zinc concentrations (●: senile cataract, △: glaucoma, +: glaucoma+cataract, ×: congenital cataract). SI conversion: μg/ml×15·3=μmol/l.

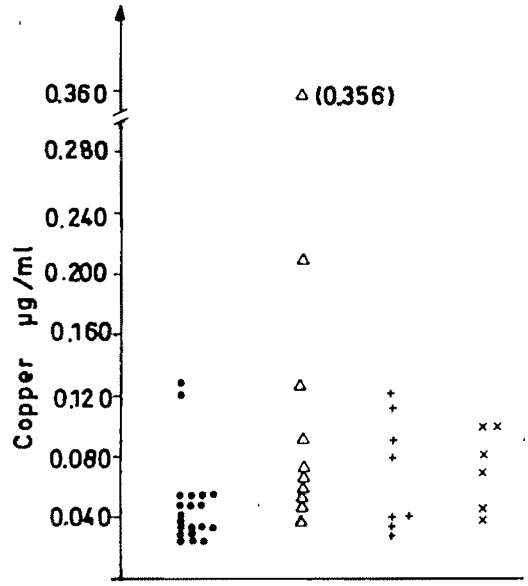


Figure 2 Distribution diagram for aqueous humour copper concentrations (legends as for Figure 1). SI conversion: µg/ml×15·7=µmol/l.

the copper concentration to be 0·018–0·080 µg/ml (0·28–1·3 µmol/l) in the aqueous humour of normal human subjects. In the present study, for the patients with cataract and glaucoma, we observed higher copper and lower zinc concentrations than the values noted above. In general, copper and zinc are reported to be metabolical antagonists.[2 7] This supports the negative correlation which we have found between the copper and zinc concentrations in the aqueous humour of the patients with glaucoma. A high copper level together with a low zinc level may be caused by the following factors: (1) abnormalities in the secretion of aqueous humour[5]; (2) difficulties in the outflow of aqueous humour through canal of Schlemm[8]; and (3) breakdown of the blood-aqueous humour barrier as a result of trauma, infection, and inflammation.[9] In normal circumstances it was found that the blood-ocular barrier effectively excludes a potentially toxic excess copper from the eye.[4] Breakdown of the barrier has been shown to result in increase of copper levels in aqueous humour, which is associated with an influx of plasma proteins into the anterior chamber.[4 10] Thus in one of our patients who had a glaucomatocyclitic crisis (Posner-Schlossman syndrome) we found an aqueous humour zinc concentration of 0·050 µg/ml (0·76 µmol/l) and copper concentration of 0·356 µg/ml (5·6 µmol/l). It has been reported that during the stress of infection or inflammation copper levels rise and zinc levels fall owing to the acute-phase reaction.[2] Moreover there may be slightly increased serum copper levels in all groups for the reasons noted above.

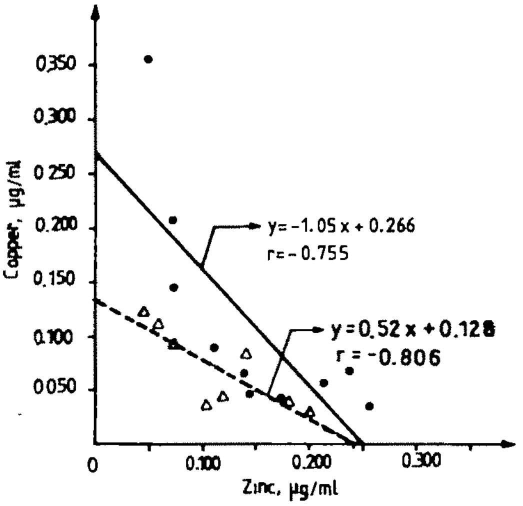


Figure 3 Regression line between aqueous humour zinc and copper concentrations (●: glaucoma, Δ: glaucoma+cataract).

According to our results here a negative correlation between aqueous humour copper and zinc levels in patients with glaucoma, especially when caused by trauma and inflammation, may be of importance. It is concluded that increase in the copper concentration in the aqueous humour may indicate a breakdown of the blood-aqueous barrier. This subject needs further investigation.

1 Eckhert CD. Elemental concentrations in ocular tissues of various species. *Exp Eye Res* 1983; 37: 639–47.
2 Jacob RA. Trace elements. In Tietz NW, ed. *Fundamentals of clinical chemistry* Philadelphia Saunders, 1987. 517–32
3 McGahan MC, Bito LZ Determination of copper concentration in blood plasma and in ocular and cerebrospinal fluids using graphite furnace atomic absorption spectroscopy. *Anal Biochem* 1983; 135: 186–92
4 Cook CS, Grubb B. Experimental hypercupremia does not result in increases in copper in levels, iris or ocular fluids *Curr Eye Res* 1986; 5: 171–3.
5 Gerhard JP, Calmé P, Kraeminger E A propos du zinc de l'humeur-aqueuse. *Klin Monatsbl Augenheilkd* 1980, 176: 652–4.
6 Moster MF, Riebel O, Komárek J Determination of copper and iron in aqueous by means of atomic absorption spectrometry *Cesk Oftalmol* 1980, 36: 190–4.
7 Oestreicher P, Cousins RJ. Copper and zinc absorption in the rat: mechanism of mutual antagonism. *J Nutr* 1985; 115: 159–66.
8 Hoskins HD, Koss M *Becker-Shaeffer's diagnosis and therapy of the glaucomas* St Louis. Mosby, 1989 41–66.
9 Caprioli J. The ciliary epithelia and aqueous humour. In: Moses RA, Hart WM, eds *Adler's physiology of the eye. Clinical Application* St Louis: Mosby, 1987: 204–22
10 McGahan MC, Bito LZ The pathophysiology of the ocular microenvironment. I. Preliminary report on the possible involvement of copper in ocular inflammation *Curr Eye Res* 1983; 2: 883–5

British Journal of Ophthalmology, 1990, 74, 663–664

Topical timolol and serum lipoproteins

James West, Simon Longstaff

Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield
J West
S Longstaff

Correspondence to:
Mr J West, Department of Ophthalmology, A Floor,
Royal Hallamshire Hospital,
Glossop Road, Sheffield
S10 2JF.

Accepted for publication
17 May 1990

Abstract

Oral timolol taken for the treatment of systemic hypertension has been shown to affect adversely serum lipoprotein levels. In a 15-week study on 19 patients topical timolol therapy for raised intraocular pressure was found to have no significant adverse effect on serum lipoprotein levels. This is reassuring in view of the large number of patients on this form of long term therapy, and selection of the type of β blocker to use should not be influenced by lipid changes associated with the oral form of the drug.

β Blockers taken orally for antihypertensive therapy have been shown in numerous studies to have a significant effect on serum lipoproteins.[1–5] Of the various types of β blockers in use those that are non-selective and without intrinsic sympathomimetic activity (ISA), such as propranolol or timolol, cause the most pronounced changes, with an average increase in serum triglycerides (TG) of 32%, while high density lipoproteins (HDL) were lowered by 16%.[1] HDL concentration bears an inverse relation to coronary heart disease, as was pointed out by Miller and Miller and since confirmed in several prospective studies.[6–9] The relation of TG concentration to coronary heart disease, however, remains unclear.[9,10]

Topical β blockers are widely used and often the first line of therapy in many patients requiring treatment for glaucoma or ocular hypertension. A large proportion of these patients are or will be on long term therapy over many years. With other systemic adverse effects from topical β blocker therapy already described,[11] we decided to carry out a prospective study using a non-selective β blocker to ascertain that a side effect on serum lipoprotein levels was not going undetected in so many patients on treatment for glaucoma.

Materials and methods

This was a prospective study to see if there was any change in serum lipoprotein levels at 5 and 15 weeks from the beginning of topical timolol therapy. Patients to be started on topical timolol for raised intraocular pressure presenting or already attending the ophthalmic outpatients department were enrolled in the study.

Procedure. A fasting lipid sample was obtained without venous stasis on the morning before starting therapy, with abstinence from alcohol the previous day. All patients were prescribed timolol 0·5% twice daily to both eyes, and repeat fasting lipid samples were taken at 5 and 15 weeks. Laboratory lipid analysis was carried out on a COBAS BIO centrifugal analyser using Technicom methodology with frequent control serum analysis. TG, HDL, and total cholesterol (TC) only were measured.

Exclusion criteria. Patients excluded were those already on oral β blockers or thiazide diuretics; those who were grossly over weight or with known hyperlipidaemias or with a family history of such; and those with obstructive air ways disease, heart block or failure, or with moderate to heavy alcohol intake.

Results

A total of 19 patients were enrolled in the study. Their mean age was 67·5 years, median 63 years, and range from 46 to 80 years. The male to female ratio was 11 to 8. All patients completed five weeks of therapy; however, two were withdrawn before 15 weeks, one because of poor compliance and the other because of drainage surgery.

Table 1 shows the mean values obtained for the various lipid fractions at baseline and at 5 and 15 weeks with standard deviations (SD), mean change, and t values. No significant change in any of the lipid fractions was observed at any time.

Retrospective analysis of the data was carried out to establish adequate study power to detect a difference from baseline of 0·3 mmol/l (minimum) in the TG fraction for a type II error of 0·1 (power 90%). The 95% confidence intervals for the true mean difference are −0·22 to 0·14 mmol/l at 5 weeks and −0·11 to 0·3 mmol/l at 15 weeks by the usual formula based on the t distribution.

Discussion

The risk of coronary heart disease is known to be influenced by blood lipid levels. There is a

Table 1 Mean values for lipid fractions with standard deviation, mean change, and t *values*

	5 weeks figures (19 patients)				*15 weeks figures (17 patients)*			
	Baseline Mean (SD)	*5 Weeks Mean (SD)*	*Difference*	t	*Baseline Mean (SD)*	*15 Weeks Mean (SD)*	*Difference*	t
TC	6·03 (0·96)	6·12 (1·08)	+0·09	0·258	5·91 (0·94)	6·11 (1·09)	−0·2	0·572
TG	1·54 (0·62)	1·505 (0·59)	−0·035	0·177	1·482 (0·49)	1·59 (0·76)	+0·108	0·494
HDL	1·45 (0·3)	1·4 (0·24)	−0·05	0·54	1·435 (0·27)	1·376 (0·26)	−0·059	0·649

TC: total cholesterol. TG triglycerides HDL high density lipoproteins significant correlation between total cholesterol and risk of disease but weak correlation between triglyceride concentration and risk.[9] Of the cholesterol subfractions, the low density lipoprotein (LDL) concentration (the main transporting lipoprotein) appears to have the most significant effect,[12-13] while HDL concentration correlates inversely with risk and would appear to be cardioprotective.[6-9] Systemic β blockers are known to affect serum lipoproteins levels adversely, the amount of change depending on the type of β blocker. Oral therapy with non-selective β blockers without ISA cause the most pronounced changes, with an average increase in serum TG concentration of 32% and lowering of HDL concentration by 16%. Selective β blockers without ISA have less pronounced effect (TG:+20%, HDL:−7%), while non-selective blockers with ISA have least effect (TG: +18%, HDL: −1%).[1]

Drug therapy for hypertension has failed to show a definite protection against coronary heart disease, and some workers consider that the benefit from blood pressure reduction may be outweighed by the adverse influence of therapy on serum lipoproteins levels.[14] Topical β blockers are now an established first line treatment in glaucoma. There is a significant incidence of systemic side effects (some serious), and, because of these, topical β blockers must be prescribed with caution in certain patients. That such small doses of drug applied to the eye can produce such systemic side effects has been attributed in part to the fact that, unlike oral β blockers, which are extensively metabolised in the liver before entering the general circulation,[15] topical β blockers are absorbed directly through the conjunctiva and nasal mucosa (first order pass). However, studies show that topically applied β blockers rarely reach serum levels normally considered therapeutic for antihypertensive treatment,[16,17] and despite this side effects are still experienced. Moreover, studies on healthy volunteers show that topical β blockers reduce exercise induced tachycardia and slightly decrease the resting pulse rate.[16,18]

Our lipid analysis at 5 and 15 weeks should detect any change in lipid fractions if present, as the change produced by oral therapy occurred by 8 weeks and was little changed thereafter. The results show no significant adverse effect on serum lipoproteins as a consequence of topical β blocker therapy. This is reassuring in view of the large number of patients on long term therapy for raised intraocular pressure, and there appears to be no justification for using selective β blockers, or those drugs with ISA, on the basis of the adverse effects on serum lipoproteins shown for the oral form of therapy.

We thank Dr R B Forrester and his staff for help with lipid analysis and Dr R A Dixon for his help in statistically analysing the results.

1 Weidmann P, Uehlinger DE, Gerber A. Antihypertensive treatment and serum lipoproteins (review). *J Hypertens* 1985; **3**: 297–306.
2 Helgeland A, Hjermann I, Leren P. High-density lipoprotein cholesterol and antihypertensive drugs: the Oslo study. *Br Med J* 1978; ii: 403.
3 Greenberg G, Brennan PJ, Miall WE. Effects of diuretic and beta-blocker therapy in the Medical Research Council trial. *Am J Med* 1984; **76**: 45–51.
4 Leren P, Olav Foss P, Nordvik B, Fossbakk B. The effect of enalapril and timolol on blood lipids. *Acta Med Scand* 1988; **223**: 321–6.
5 Pasotti C, Capra A, Florella G, Vibelli C, Chierichetti SM. Effects of pindolol and metoprolol on plasma lipids and lipoproteins. *Br J Clin Pharmacol* 1982; **13**: 435s–9s.
6 Miller GJ, Miller NE. Plasma high density lipoprotein concentration and the development of ischaemic heart disease. *Lancet* 1975; i: 16–9.
7 Kannel WB. High density lipoproteins: epidemiologic profile and risks of coronary artery disease. *Am J Cardiol* 1983; **52**: 9–12B.
8 Gordon T, Castelli WP, Hjortland MC, *et al*. High density lipoprotein cholesterol as a protective factor against coronary heart disease. The Framingham study. *Am J Med* 1977; **62**: 707–14.
9 Pocock SJ, Shaper AG, Phillips AN. Concentration of high density lipoprotein cholesterol, triglycerides, and total cholesterol in ischaemic heart disease. *Br Med J* 1989; **298**: 998–1002.
10 Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J* 1986; **112**: 432–7.
11 Fraunfelder FT, Meyer SM. Systemic adverse reactions to glaucoma medications. *Int Ophthalmol Clin* 1989; **29**: 143–6.
12 Consensus Development Panel. Lowering blood cholesterol to prevent heart disease. *JAMA* 1985; **253**: 2080–6.
13 Study Group of the European Atherosclerosis Society. *Eur Heart J* 1987; **8**: 77–88.
14 Houston MC. New insights and new approaches for the treatment of essential hypertension. *Am Heart J* 1989; **117**: 911–51.
15 Tocco DJ, Duncan AEW, Deluna FA, *et al*. Physiological disposition and metabolism of timolol in man and laboratory animals. *Drug Metab Dispos* 1975; **3**: 361–70.
16 Affrime MB, Lowenthal DT, Tobert JA, *et al*. Dynamics and kinetics of ophthalmic timolol. *Clin Pharmacol Ther* 1980; **27**: 471–77.
17 Passo MS, Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. *Ophthalmology* 1984; **91**; 1361–3.
18 Brazier DJ, Smith SE. Ocular and cardiovascular response to topical cartelol 2% and timolol 0·5% in healthy volunteers. *Br J Ophthalmol* 1988; **72**: 101–3.

For those patients who should avoid taking nonselective ocular beta blockers...

“Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

A bright outlook for glaucoma patients

For effective control of IOP minimising the risks associated with nonselective beta-blockade [2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only β_1 selective ocular beta blocker

SELECTIVE β_1 BETA-BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased co sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depre neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies not demonstrated any specific hazard there are no adequate and well-controlled studies in preg women. Because animal studies are not always predictive of human response this drug should be during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known wh Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is adminis to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml droptainer **PRODUCT LICE HOLDER AND NUMBER:** Alcon Laboratories U.K 0649/0097. DATE OF PREPARATION: JANUARY

Further information is available on request

Alcon

SPECIALISTS IN EYE CARE

Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

REFERENCES:

1. Jones FL, Ekberg NL. Letter N Eng J Med 1979; **301**: 270.
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62.
3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92.
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

British Journal of Ophthalmology, 1990, 74, 665–669

Haemorheological changes in patients with retinal vein occlusion after isovolaemic haemodilution

J Wiek, M Schade, M Wiederholt, H R Arntz, L L Hansen

Abstract

In 83 patients with central retinal vein occlusion and branch vein occlusion we measured the haematocrit (HCT), plasma viscosity (PV), red cell aggregation (RCA), red cell filterability (RCF) and apparent whole blood viscosity (WBV). A control group (n=41) was matched for sex, age, and cardiovascular risk factors. Measurements were performed before and after treatment with isovolaemic haemodilution (IHD). We found no significant differences between patients with retinal vein occlusion (RVO) and control subjects in haematocrit, plasma viscosity, red cell aggregation, and red cell filterability and no increased whole blood viscosity in the patient group. Patients with ischaemic retinal vein occlusion and non-ischaemic retinal vein occlusion did not show different haemorheological parameters either. After treatment with haemodilution, only the haematocrit and whole blood viscosity were significantly decreased, and there were no changes in plasma viscosity, red cell aggregation or red cell filterability.

Some studies[1–4] have shown that impaired blood rheology might have a role in the pathogenesis of retinal vein occlusion (RVO). The authors reported an increased haematocrit and whole blood viscosity in patients with retinal vein occlusion[2] or ischaemic retinal vein occlusion.[1,3] In addition in all patients with retinal vein occlusion the plasma viscosity was found to be raised[1,2,4] and red cell filterability to be decreased.[4] So far no studies of red cell aggregation have been done in patients with retinal vein occlusion.

Several studies have stressed the role of haemorheology by demonstrating that isovolaemic haemodilution (IHD) is a beneficial for patients with this disease.[5–9] However, some important questions remain unanswered:

(1) How do patients with retinal vein occlusion compare with subjects of the same age and sex with the same prevalence of cardiovascular risk factors in terms of haemorheology?

(2) Do basic haemorheological parameters differ in patients with different types of retinal vein occlusion (ischaemic versus non-ischaemic), as has been found by some authors?[1,3]

(3) Can the beneficial effects of haemodilution in the treatment of retinal vein occlusion be correlated with a higher blood fluidity?

We measured the basic rheological parameters haematocrit, plasma viscosity, red cell aggregation, red cell filterability, and also the apparent whole blood viscosity in patients with central retinal vein occlusion (CRVO) and branch vein occlusion (RBVO) in comparison with a control group matched for sex, age, and cardiovascular risk factors without vascular diseases of the eye. In addition we determined these parameters in patients with retinal vein occlusion after treatment by isovolaemic haemodilution.

Steglitz Clinic, Free University of Berlin, University Eye Clinic
J Wiek
L L Hansen

Institute for Clinical Physiology
M Schade
M Wiederholt

Medical Clinic
H-R Arntz

Correspondence to
Dr J Wiek, Universitats-Augenklinik Freiburg,
Killianstrasse 5, 7800
Freiburg, West Germany.

Accepted for publication
31 May 1990

Subjects and methods

All patients with recent retinal vein occlusion (less than eight weeks' duration of symptoms) referred to the Eye Clinic, Klinikum Steglitz, Free University of Berlin, between July 1984 and December 1986 were considered for a prospective trial. Patients with systemic diseases such as congestive heart failure unresponsive to treatment, renal and respiratory insufficiency, and anaemia (haematocrit below 38%) were excluded from the study.[6,8,10] We included 66 patients older than 50 years of age and 17 patients of 30 to 50 years of age (Table 1). The patients of two randomised controlled studies on isovolaemic haemodilution[8,10] were also included.

The control subjects were divided into two age and sex matched groups of 30 to 50 years and older than 50 years. The first group was recruited from healthy colleagues of our clinic. The older group was recruited from patients without vascular diseases of the eye who had to undergo surgery for cataract or retinal detachment. This group was matched for cardiovascular risk factors.

Every patient underwent a physical examination, electrocardiography (ECG), and chest *x* ray, together with basic laboratory tests and measurement of fibrinogen. In addition the patients were submitted to a detailed ophthalmological examination, funduscopy, and fluorescein angiography.

We classified the retinal vein occlusions into ischaemic and non-ischaemic types.[8–10] At least two of the following conditions had to be fulfilled to allow the diagnosis of an ischaemic central retinal vein occlusion: (1) Fluorescein angiogram: time for maximal venous filling (t_{mvf}) ≥ 20 s. (2) Capillary occlusion: area of ≥ 1 papilla diameter (PD) and/or ≥ 10 cotton-wool spots. (3) Visual acuity: $\leq 6/60$.

Table 1 Subdivision of patients

Age	*Type*	*Treatment*	*Total*	*Women*	*Men*
30–50	*CRVO*	*IHD*	*17*	*10*	*7*
>50	RVO	IHD	36	18	18
	RBVO	IHD	11	7	4
	CRVO	IHD	25	11	14
>50	RVO	no IHD	30	17	13
	RBVO	no IHD	17	8	9
	CRVO	no IHD	13	9	4

RVO=retinal vein occlusion. RBVO=retinal branch vein occlusion CRVO=central retinal vein occlusion with and without isovolaemic haemodilution (IHD)

A branch vein occlusion was regarded to be ischaemic if it had at least three cotton-wool spots and/or a capillary occlusion area of one PD or more. The procedure for isovolaemic haemodilution has been described elsewhere.[6 8 9]

As venous occlusion in younger patients may often be due to inflammatory changes in ophthalmic veins,[11] all patients younger than 50 years were additionally treated with systemic steroids (75 mg of prednisolone daily) for one week, with subsequent tapering over 3–5 weeks. Patients with ischaemic CRVO were photocoagulated to prevent neovascular glaucoma and retinal neovascularisation.[6 9]

RHEOLOGICAL MEASUREMENTS

The venous blood for rheological measurements was drawn from an antecubital vein without stasis and immediately collected into test tubes containing EDTA as anticoagulant.

The haematocrit was evaluated by centrifugation at 15 000 g for five minutes (micromethod).

Plasma viscosity was measured at 37°C after centrifugation (3000 *g* for 10 minutes) with an Ubbelohde capillary viscosimeter.[12] The measurement was repeated five times. The data are given in cm^2/s=centistokes (cSt).

The determination of the red cell aggregation was done with a Myrenne aggregometer[13] with a natural (unchanged haematocrit) and with a standardised blood sample (haematocrit: 40%). At first our investigations were done at a shear rate of 460/s for 10 s to disaggregate the blood and then measured at a stop of 0/s. After a modification of the Myrenne aggregometer (modernisation to allow two different measurements) the blood was disaggregated at a rate of 600/s for 5 s, and then red cell aggregation was measured at (1) a stop to 0/s and (2) after a reduction to 3/s. The measurements of the new and the old method are not comparable. Values are without dimension.

For measuring the red cell filterability we used a Myrenne MF4 with nucleopore filters of 5 μm pore diameter of one single batch. By this method it is possible to detect changes in red cell filterability in four of five stress models.[14] The blood sample was washed twice in a special phosphate buffered human albumin solution and diluted with this buffer to a haematocrit of 4%. Our results show the inital slope (initial rise of flow curve, after 10% of the blood sample has passed the nucleopore filter). We think that these early values are only mildly affected by clogging of the nucleopore filters with white blood cells.[14] We measured two blood samples from each patient using new nucleopore filters for each measurement.

Apparent whole blood viscosity was measured at 37°C with a Wells-Brookfield cone plate microviscometer Model LVT[15] at shear rates of 230, 115, 46, and 23 $s,^{-1}$ Measurements at lower shear rates (11·5 and 5·75 s^{-1}) were discarded, because they are less reliable.[3 16 17] We determined whole blood viscosity in a native blood sample and a standardised blood sample with a haematocrit of 40%. All measurements were repeated twice. The data are given in g/cm×s=centipose (cP). Theoretically it should not be necessary to determine the whole blood viscosity, as the haematocrit, the plasma viscosity, the red cell aggregation, and the red cell filterability are the basic parameters of blood viscosity. Nevertheless, we evaluated whole blood viscosity to circumvent the uncertainties in the determination of red cell aggregation and red cell filterability by including an additional parameter and also to be able to compare our results with those of other authors,[1-3] who relied mainly on whole blood viscosity.

The statistical variation of the results is expressed as the standard deviation about the mean. Student's *t* test was used for comparison of two means. Significant differences were considered to be present with $p<0{\cdot}05$.

Results

Control subjects and patients over 50 years of age showed the same prevalence of cardiovascular risk factors. 55% of control subjects and 54% of the patients with retinal vein occlusion had at least two of the following risk factors: hypertension (>160/90 mm Hg), smoking, obesity, hyperlipoproteinaemia, cardiovascular diseases (for example, history of myocardial or cerebral infarction, angina pectoris, transient ischaemic attacks), diabetes mellitus.

CONTROL GROUP

Table 2 shows the results of haemorheological measurements in control subjects of 30–50 years and > 50 years. Age distribution was similar in men and women. There were no age dependent differences in the haematocrit (HCT) within the groups of the same sex. However, women of both age groups had a significantly lower haematocrit than men. The plasma viscosity (PV) of men and women did not differ, but younger men had a lower plasma viscosity than older ones. The red cell aggregability (RCA) of women aged 30–50

Table 2 Rheological data of control subjects

		F>50	*F 30–50*	*M>50*	*M 30–50*
Age (years)	Mean	72·3	39·1	65·6	41 2
	SD	8·4	7·2	9 8	6·3
	n	9	12	10	10
HCT (%)	Mean	41·8	41·6	46 4**	44·3**
	SD	2·3	1·8	3·6	2 8
	n	9	12	10	10
PV (cSt)	Mean	1·35	1·29	1 40+	1 28
	SD	0·11	0 05	0 1	0·06
	n	9	12	10	10
RCA	Mean	18·1	13 4*	17 1	18 8
	SD	5·2	2·2	3·1	3 9
	n	4	8	6	8
RCF	Mean	27 4	21·6	24·6	25 0
	SD	5 5	8 0	9 4	8 6
	n	6	12	10	7
WBV 230/s (cP)	Mean	4 6	4 0++	5·0	4·7***
	SD	0·5	0·3	0·8	0·3
	n	9	12	10	10
WBV 23/s	Mean	6 9	6 1	8·0*	7 0**
	SD	1 4	0 9	1·3	1 0
	n	9	12	10	10

Mean values of age, haematocrit (HCT), plasma viscosity (PV), red cell aggregation (RCA), red cell filterability (RCF), and whole blood viscosity (WBV – 230/s and 23/s) depending on age (>50, 30–50) and sex (F, M) Significant differences are given between groups of same age and different sex (*$p<0{\cdot}05$, **$p<0\ 01$, ***$p<0\ 001$) and groups of same sex and different age (+$p<0\ 05$, ++$p<0\ 01$, +++$p<0\ 001$) RCA was measured after disaggregation with a shear rate of 460/s and a stop to 0/s.

years was significantly lower than in men of the same age. There were no age related differences within the groups of men and women. Table 2 gives the results of the old method before modification of the aggregometer; all other tables show the results of the new method after a stop to 0/s. Red cell filterability was not dependent on age or sex. Measurements of whole blood viscosity revealed a higher fluidity in women aged 30–50 years than in the group of >50 years at a high shear rate, probably depending on a slightly lower plasma viscosity and a decreased red cell aggregation in this age group. Correspondingly, men of the younger age group in comparison with the younger women had higher whole blood viscosity at the shear rates of 230/s and 23/s, Men over 50 had higher whole blood viscosity only at the shear rate of 23/s. These differences may be due to the higher haematocrit of men. Our tables show the results of the natural (unchanged haematocrit) blood samples.

PATIENTS WITH RETINAL VEIN OCCLUSION

Table 3 shows the mean values of rheological data in patients with retinal vein occlusion divided by age and sex. We found significant differences between patients and control subjects only in whole blood viscosity at a shear rate of 230/s. Women >50 years and men of 30–50 years had lower whole blood viscosities than corresponding control groups. When dividing retinal vein occlusion into ischaemic and non-ischaemic types in the group older than 50 (the number of the group aged 30–50 years of age was too small to make this division), we found no significant differences between the two types in any of our measurements (Table 4). Nor did we find significant differences between patients with retinal branch vein occlusion and patients with central retinal vein occlusion.

Table 3 Rheological data of patients with RVO dependent on age and sex

		Women			*Men*		
		Mean	*SD*	*n*	*Mean*	*SD*	*n*
Age	RVO 30–50	44·8	4·7	10	44·9	2·6	7
	RVO>50	68·3	8 4	35	63·0	8·9	31
HCT	RVO 30–50	42·5	3·0	11	43·9	2·3	8
(%)	RVO>50	41·7	2·3	35	44·8	3·4	31
PV	RVO 30–50	1·30	0·08	11	1 32	0·08	8
(cSt)	RVO>50	1·35	0·08	35	1·35	0·09	31
RCA	RVO 30–50	6·3	1·1	7	6·3	1·5	5
	RVO>5	8·0	1 7	18	7·2	1·9	17
RCF	RVO 30–50	20·7	6·9	10	24·1	2·2	7
	RVO>5	23 9	5·5	32	24·1	7·0	28
WBV	RVO 30–50	4·2	0·5	11	4·3*	0·2	8
230/s	RVO>50	4·1**	0·4	34	4·6	0·5	30
(cP)							
WBV	RVO 30–50	6·4	1·0	11	6·6	0·7	8
23/s	RVO>50	6·3	0·8	34	7·3	1·1	30

30–50 and >50 refers to the age group. Significant differences (*p<0·05, **p<0·01) refer to corresponding control subjects For other abbreviations see Table 2. RCA was measured with the new method (shear rate of 600/s and then stop to 0/s.)

Table 4 Rheological data of patients over 50 years of age with RVO dependent on the type of occlusion

		Women>50			*Men>50*		
		Mean	*SD*	*n*	*Mean*	*SD*	*n*
Age	RVO i	65 5	7·4	13	60·2	8·5	17
	RVO ni	69·9	8·7	22	66·4	8·4	14
HCT	RVO i	41·1	1·8	13	44·4	3·6	17
(%)	RVO ni	42·0	2·5	22	45·2	3·1	14
PV	RVO i	1·32	0·09	13	1·33	0·08	17
(cSt)	RVO ni	1·36	0·07	22	1·37	0·09	14
RCA	RVO i	6·9	1·5	5	6·9	1·8	10
	RVO ni	8·4	1·7	13	7·7	2·2	7
RCF	RVO i	23·9	5·9	11	23·5	8·1	17
	RVO ni	23·8	5·4	21	25·1	5·0	11
WBV	RVO i	4 1	0·3	13	4·5	0·4	17
230/s	RVO ni	4·2	0·4	21	4·7	0·5	13
(cP)							
WBV	RVO i	6·0	0·7	13	7·2	1·3	17
23/s	RVO ni	6·5	0·9	21	7·5	1·0	13

i=Ischaemic, ni=Non-ischaemic. For other abbreviations see Table 2.

ISOVOLAEMIC HAEMODILUTION

Tables 5 and 6 and Fig 1 depict the results of patients with retinal vein occlusion before and after haemodilution. All four groups show significant differences in haematocrit and whole blood viscosity (230/s and 23/s) before and after haemodilution, but no changes of plasma viscosity, red cell aggregation, or red cell filterability.

Discussion

The interpretation of basic rheological parameters in patients with disturbed retinal circulation requires carefully selected and matched control subjects. In addition, one has to avoid methodological problems, especially in the determination of red cell aggregation and red cell filterability. Our patients and control subjects were properly matched by sex, age, and, most important, cardiovascular risk factors. Nevertheless it seems useful to compare the values obtained from our control subjects with measurements provided by other studies.[18] As expected, the haematocrit values confirmed the independence of age and the dependence on sex, as other authors have shown.[18, 19]

The plasma viscosity proved to be independent of sex, but men over 50 had a higher plasma

Table 5 Rheological data of women with RVO before and after isovolaemic haemodilution

	Before IHD			*After IHD*			
	Mean	*SD*	*n*	*Mean*	*SD*	*n*	*p≤*
Women 30–50							
HCT	42·1	3·7	7	36·1	3·6	6	0·05
PV	1·29	0·1	7	1·32	0·11	6	ns
RCA	6·2	0·9	4	5·9	0·9	3	–
RCF	21·9	6·8	6	23·6	5·7	5	ns
Women <50							
HCT	41·8	2·3	18	35·8	4·8	17	0·01
PV	1·34	0·09	18	1·31	0 09	17	ns
RCA	7·8	1·9	7	7·0	2·1	6	ns
RCF	21·7	4·9	16	20·0	7·6	16	ns

For abbreviations see Table 2.

Table 6 Rheological data of men with RVO before and after isovolaemic haemodilution

	Before IHD			*After IHD*			
	Mean	*SD*	*n*	*Mean*	*SD*	*n*	*p≤*
Men 30–50							
HCT	43·8	2·4	7	36	2·5	7	0·01
PV	1·31	0·09	7	1·33	0·08	7	ns
RCA	6·3	1·5	5	6·2	0·9	5	–
RCF	24·5	2·1	6	19·6	9 9	7	ns
Men <50							
HCT	44·6	3·5	18	35·5	4·0	18	0·01
PV	1·35	0·09	18	1·34	0·09	18	ns
RCA	7·4	2·1	8	6·9	2·1	10	ns
RCF	23·6	7·8	16	26 1	7·3	15	ns

For abbreviations see Table 2.

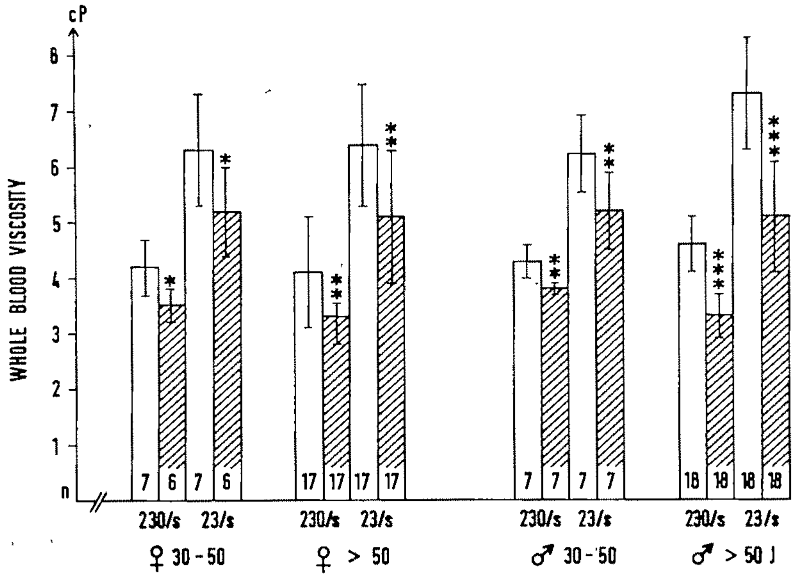


*Figure 1 Decrease of whole blood viscosity after haemodilution (hatched bars) in men and women in the two different age groups. 230/s and 23/s=shear rates. *p<0·05, **p<0·01, ***p<0·001.*

viscosity than younger men. Lowe and Forbes[20] also reported a significant increase of plasma viscosity in older people. On the other hand Jung *et al* 1986 found neither a sex nor an age dependence of plasma viscosity. A reason for this discrepancy may be a different prevalence of cardiovascular risk factors, which were absent in the subjects studied by Jung *et al.*[18] It is known that cardiovascular diseases and even hypertension increase the plasma viscosity.[12 21]

Red cell aggregation was lower in women than in men between 30 and 50 years. This contrasts with the results of Jung *et al*[18] who found no sex dependence with the Mini Erythrozyten-Aggregometer in age groups of healthy volunteers over 30 years.

Measurements of the filterability of erythrocytes are still a matter of much controversy[22-25] and can only be tentatively interpreted. We do not know whether our in-vitro test reflects the in-vivo behaviour of red cells in the microcirculation. The technical problem of standardised filters has not yet been solved. Furthermore the role of artefacts caused by washing procedures to reduce the leucocyte concentration is not known. Our study of red cell filterability in control subjects did not reveal any age or sex dependence, which is in accordance with the data given by Jung *et al,*[18] but it has to be noted that these authors used the single erythrocyte rigidometer.

In general, we found no differences in basic haemorheological parameters between patients with retinal vein occlusion and control subjects of the same age and the same prevalence of cardiovascular risk factors. In addition, no haemorheological differences could be detected between patients with ischaemic and non-ischaemic retinal vein occlusion.

In contrast to Ring *et al*[2] and Trope *et al*[3] we found no higher haematocrit values in patients with retinal vein occlusion, but those authors did not take into account the distribution of men and women. Ring *et al* did not state the sex distribution, and Trope *et al* had a higher percentage of men than women in the ischaemic group (65% vs 36% in non-ischaemic RVO), which might account for a higher haematocrit. Correspondingly the same authors found higher whole blood viscosity in patients with ischaemic retinal vein occlusion. Peduzzi *et al*[4] found increased whole blood viscosity in all patients with retinal vein occlusion at a shear rate of 23/s. We have no explanation for these differences in our results, as Peduzzi used the same methods as we did. McGrath *et al*[5] found higher whole blood viscosity in 53% of their patients with retinal vein occlusion, but they used considerably lower shear rates for their investigations, so that their results are not comparable with ours.

As to the plasma viscosity, we could not confirm the results of earlier investigations,[1-3] as we did not find raised plasma viscosities in RVO patients. Dodson *et al*[26] found raised plasma viscosities in patients with retinal vein occlusion only in comparison with controls without hypertension. It is known that cardiovascular risk factors can lead to an increase of plasma viscosity and other rheological parameters.[12 21] This may explain why our patients with retinal vein occlusion had similar values of plasma viscosity as control subjects, as we had almost the same prevalence of at least two cardiovascular risk factors (about 55%) in both groups. If one compares our numerical values of plasma viscosity with those of a healthy reference population without cardiovascular risk factors, as investigated by Jung *et al*[18] the plasma viscosity of our groups seems to be raised. So it is not surprising that people with retinal vein occlusion and risk factors have increased plasma viscosity in comparison with controls without risk factors.

Until now there have been no investigations into red cell aggregation in patients with retinal vein occlusion. Because the method was changed we unfortunately have only small numbers of comparable patients and control subjects, but between these small groups we found no significant differences.

Peduzzi *et al*[4] reported decreased red cell filterability in patients with retinal vein occlusion. However, they used the method of whole blood filtration,[27] which can no longer be regarded as a reliable method for red cell filtration.[25]

Haemodilution by definition decreases the haematocrit and hence should lower whole blood viscosity. This could be demonstrated in all haemodiluted patients. The increased fluidity of the whole blood was induced only by reduction of the haematocrit. All other basic rheological parameters remained unchanged by haemodilution. Kiesewetter *et al*[28] have shown, albeit using different methods, that red cell filterability was increased and red cell aggregation reduced by a combination of iso- and hypervolaemic haemodilution in patients with peripheral arterial occlusive disease. This was not confirmed by Heinen *et al*[7] in patients with retinal vein occlusion, who reported no change of red cell filterability after haemodilution and an increase of red cell filterability after hypervolaemic haemodilution. Our finding of an unchanged plasma viscosity is supported by both studies.[7 28]

In conclusion, our study has demonstrated that patients with retinal vein occlusion do not have a different haemorheological profile when compared with control subjects matched for age, sex, and risk factors. Furthermore, the determination of plasma viscosity, red cell aggregation, red cell filterability, and haematocrit does not help in the clinically important differential diagnosis of ischaemic versus non-ischaemic retinal vein occlusion. But the measurement of the haematocrit remains necessary, as this value is important for monitoring the isovolaemic haemodilution. Lack of measurable systemic rheological abnormalities does not exclude local changes of fluidity in retinal vein occlusion, which becomes obvious by fluorescein angiography.[8–10] Furthermore, haemodilution improves the visual outcome of many patients with retinal vein occlusion[6 7 9 10] by improving the retinal microcirculation, as has been shown by a decrease of time of maximal venous filling.[8–10] These beneficial effects of haemodilution may be mediated by a decreased blood viscosity.

This study was supported by the Deutsche Forschungsgemeinschaft (grant Ga 225/1–6)

1 Ring CP, Pearson TC, Sanders MD, Wetherley-Mein G Viscosity and retinal vein thrombosis. *Br J Ophthalmol* 1976; 60: 397–410.
2 McGrath MA, Wechsler F, Hunyor ABL, Penny R. Systemic factors contributory to retinal vein occlusion. *Arch Inter Med* 1978, 138: 216–20.
3 Trope GE, Lowe GDO, Meardle BM, *et al.* Abnormal blood viscosity and haemostasis in long-standing retinal vein occlusion. *Br J Ophthalmol* 1983; 67: 137–42
4 Peduzzi M, Debbis A, Guerrierri F, Bolzani R. Abnormal blood viscosity and filterability in retinal vein occlusion. *Clin Hemorheol* 1984, 4: 555–61.
5 Wiederholt M, Leonhardt H, Schmid-Schonbein H, Hager H Die Behandlung von Zentralvenenverschlussen und Zentralarterienverschlussen mit isovolamischer Hamodilution. *Klin Monatsbl Augenheilkd* 1980; 177: 157–164.
6 Hansen LL, Danisevskis P, Arntz HR, Hovener G, Wiederholt M. A randomised prospective study on treatment of central retinal vein occlusion by isovolaemic haemodilution *Br J Ophthalmol* 1985; 69: 108–16
7 Heinen A, Brunner R, Hossmann V, Konen W, Roll K, Warer T. Different types of therapy having hemorheological effects in patients with impairment of blood supply to the retina (randomised double blind study). *Clin Hemorheol* 1986, 6: 61–71.
8 Hansen LL, Wiek J, Wiederholt M. A randomised prospective study of treatment of non-ischaemic central retinal vein occlusion by isovolaemic haemodilution *Br J Ophthalmol* 1989; 73: 895–899.
9 Hansen LL, Wiek J, Schade M, Muller-Stolzenburg N, Wiederholt M Effects and compatibility of isovolaemic haemodilution in the treatment of ischaemic and non-ischaemic central retinal vein occlusion *Ophthalmologic* 1989, 199: 90–9
10 Hansen LL, Wiek J, Arntz HR. Randomisierte Studie zur Wirkung der isovolamischen Hamodilution bei retinalen Venenastverschlussen *Fortschr Ophthalmol* 1988; 85· 514–6.
11 Hayreh SS So-called central retinal vein occlusion I Pathogenesis, terminology, clinical features *Ophthalmologica* 1976, 172: 1–13
12 Leonhardt H, Uthoff A, Uthoff C. Vollblut- und Plasmaviskositat bei koronaren Risikofaktoren *Klin Wochenschr* 1977, 55: 481–5.
13 Kiesewetter H, Radtke H, Schneider R, Mussler K, Scheffler A, Schmid-Schobein H Das Mini-Erythrozyten-Aggregometer· Ein neues Gerat zur schnellen Quantifizierung des Ausmasses der Erythrozytenaggregation. *Biomed Tech (Berlin)* 1982; 27: 209–13.
14 Seiffge D Correlation of different methods to determine red blood cell deformability *Clin Hemorheol* 1984, 4. 263–73
15 Wells RE, Denton R, Merrill EW Measurement of viscosity of biologic fluids by cone plate viscometer *J Lab Clin Med* 1961; 57: 646
16 Ernst E, Matrai A Rotationsviskometer in Hämorheologie *Arztl Lab* 1982; 28: 33–8
17 Inglis TCM, Carson PJ, Stuart J Clinical measurement of whole-blood viscosity at low-shear rates *Clin Hemorheol* 1981 1: 167–77
18 Jung F, Kiesewetter H, Roggenkamp HG, *et al* Bestimmung der Referenzbereiche rheologischer Parameter. Studie an 643 zufällig ausgewahlten Probanden im Kreis Aachen *Klin Wochenschr* 1986; 64: 375–81
19 Shahidi NT. Androgens and erythropoesis *N Engl J Med* 1973, 269: 72
20 Lowe GDO, Forbes CD Blood rheology and thrombosis *Clin Haematol* 1981, 10: 343–367
21 Letcher RL, Chien S, Pickering TG, Sewley JE, Laragh JH Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects *Am J Med* 1981, 70: 1195–9
22 Chien S Principles and techniques for assessing erythrocyte deformability *Blood Cells* 1978, 3: 71–76
23 Meiselman HJ Measures of blood rheology and erythrocyte mechanics In Codelett GR Meiselman HJ, Brooks DE, eds. *Erythrocytes mechanics and blood flow* New York Springer, 1980: 75–80
24 Dormandy J. Clinical relevance of filtration tests In Dormandy J, ed *Red cell deformability and filterability* Den Haag· Nijhoff, 1983· 176–82.
25 Chien S. Specific recommendations for filtration tests In Dormandy J, ed. *Red cell deformability and filterability* Den Haag· Nijhoff, 1983· 216
26 Dodson PM, Galton DJ, Hamilton AM, Blach RK Retinal vein occlusion and the prevalence of lipoprotein abnormalities *Br J Ophthalmol* 1982, 66: 161–4
27 Reid HL, Barnes AJ, Lock PJ, Dormandy JA, Dormandy TL A simple method for measuring erythrocytes deformability *J Clin Pathol* 1976; 29: 855–8.
28 Kiesewetter H, Jung F, Lazar H, Roggenkamp HG, Leipnitz G, Kiehl R Hematocrit as a risk for vascular disease *Klin Wochenschr* 1986; 64: 974–8

British Journal of Ophthalmology, 1990, **74**, 670–675

Cytopathology of adenovirus keratitis by replica technique

Prabhat C Maudgal

Abstract

Corneal replicas were made from the severely affected eyes of 12 patients presenting with typical signs and symptoms of epidemic keratoconjunctivitis. Adenovirus was isolated from the eyes. Histopathological study of the replicas and cytology of diseased cells removed with the replica showed diffuse mild oedema of the epithelium, with scattered moderately swollen and deformed cells. The clinically observed punctate lesions histologically consisted of markedly swollen cells that had become oval or rounded. Fusion of these cells led to small syncytial formations, and the development of pseudopodia-like processes was occasionally observed. Loss of cell contents resulted in the formation of plicae on the surface of many cells. Two types of inclusion bodies were detected in the epithelial cells. The first type, intranuclear vacuolar inclusions, contained homogeneous material. The second type of inclusions were round, dense bodies, that developed in the homogeneous material of intranuclear vacuolar inclusions. The dense bodies contained the replicating and maturing virus particles. After cell degeneration the dense bodies become extracellular. Making a corneal replica had a beneficial effect on the clinical course of adenovirus keratitis.

The in vivo corneal replica technique[1-3] was developed to study the histopathology of superficial corneal lesions in different types of keratitis without disturbing the exact position of the epithelial cells in relation to each other, as this technique permits us to make an imprint of the corneal surface. In addition, in contrast to the normal cells, diseased superficial cells are easily removed with the replica. Flat mounts of these cells allow study of their cytological details.*

Previous reports on this technique from our laboratory have described the histology and histochemistry of normal superficial corneal epithelium,[4] the replicative stages of the herpes simplex virus type 1 (HSV-1) in vivo,[5] and the morphological and histochemical alterations in the HSV-1 infected rabbit epithelium.[6] These studies have not only confirmed the observations on HSV-1 replication in vitro,[7] they have also further elucidated the process of virus release from the cells after viral multiplication. Similar cytopathological alterations were detected when human dendritic and punctate lesions were investigated by means of corneal replicas.[8,9]

In this paper the cytopathology of adenovirus keratoconjunctivitis (epidemic keratoconjunctivitis) is presented. The results will be discussed in relation to the similarities to or distinguishing features from the histopathology of human dendritic and punctate herpetic keratitis, also studied by the replica technique.

Subjects and methods

Corneal replicas were made from the more severely affected eye of 12 patients who presented with the typical signs and symptoms of epidemic keratoconjunctivitis. The criterion of patient selection was the presence of epithelial punctate corneal lesions (Fig 1). Before the replica was made conjunctival swabs were taken for virus culture, and conjunctival scrapings were made. The scrapings were stained with Giemsa stain and examined by light microscopy. The technique of making a replica has been described in detail elsewhere.[1-3] In short, the procedure is as follows: (*a*) instil one drop of a topical anaesthetic three times at five minute intervals; (*b*) keep the eye open with an ocular speculum; (*c*) dry the tear film by blowing air for about one minute; (*d*) paint a thin layer of collodion in amyl acetate (3%–4% solution, w/v)

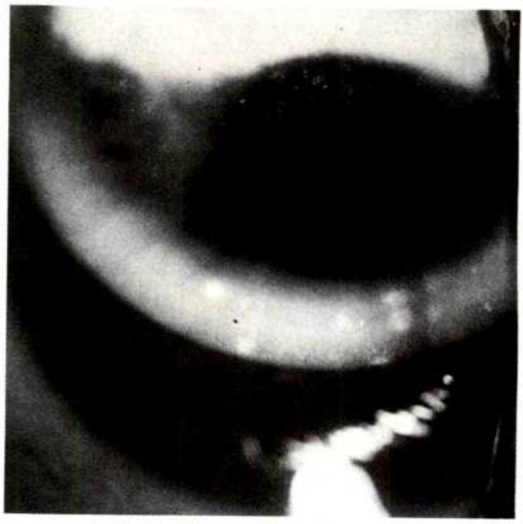


Figure 1 Punctate lesions on the cornea in epidemic keratoconjunctivitis caused by adenovirus. There is some subepithelial opacification.

Eye Research Laboratory, Division of Ophthalmology, Catholic University of Leuven, Leuven, Belgium
P C Maudgal

Correspondence to:
Dr P C Maudgal,
UZ St Rafaël, Department of Ophthalmology,
Kapucijnenvoer 33, B 3000 Leuven, Belgium.

Accepted for publication
31 May 1990

---

*The term 'replica' is used because primarily an imprint of the corneal surface is obtained with this technique. The removal of diseased cells is a secondary phenomenon. Only grossly altered cells come off with the replica. The normal corneal surface cells can be stripped off only by modifying the technique. To understand the difference consider the following: Fig 2 is mainly an imprint, therefore a replica. Only a few cells, like those shown in Fig 6, were present in this area after dissolving the replica. Figs 3 and 4 are the photographs of the replicas showing the morphology of punctate lesions surrounded by the superficial epithelial cells. Fig 5 is a low power photomicrograph of a flat mount that shows the number of 'diseased cells' forming several punctate lesions. Only a few scattered 'diseased cells' came off with the replica in the area intervening between the punctate lesions. Comparison of these photographs demonstrates the small number of cells that are actually obtained with this technique. Although the number of cells in flat mounts is small, we can stain them by conventional techniques. The replicas cannot be stained.

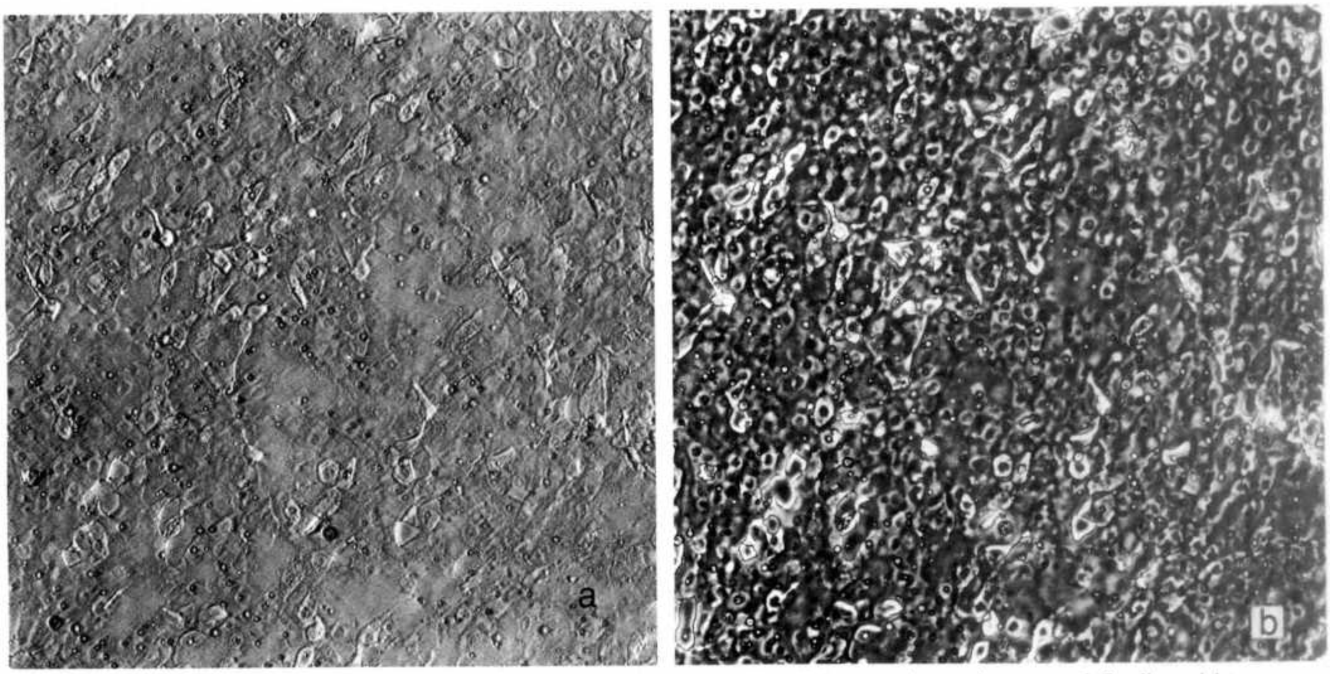


Figure 2 Scattered moderately swollen epithelium cells show morphological alterations. The cells have a tendency to become round. Small round dots are artefacts in the replica (a) Oblique illumination microscopy. (b) Phase contrast microscopy. (×180)

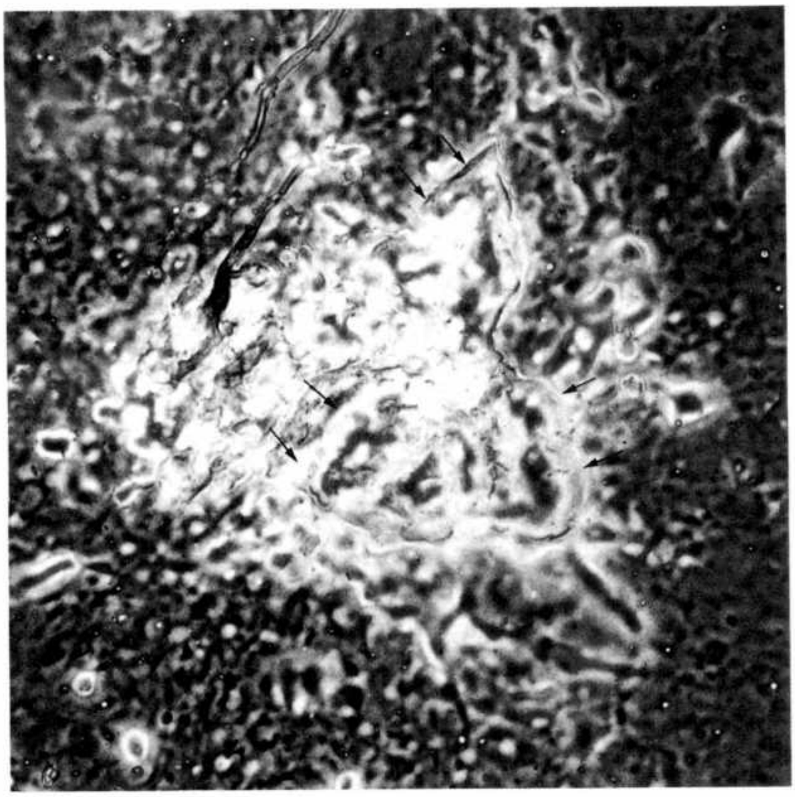


Figure 3 A focal punctate lesion appears bright in contrast to the surrounding cells. The lesion is formed by markedly swollen cells and syncytia (arrows). The borders of the lesion are irregular and not circumscribed. Phase contrast microscopy of the replica (×180)

on the cornea; (*e*) dry the painted solution by blowing air for about two minutes; (*f*) peel off the collodion membrane formed on the cornea (this is the replica of the corneal surface); (*g*) mount the membrane (replica) on clear glass slide in 0·1% albumin, with the epithelium side down. Normal cells or slightly altered cells are not removed with the replica.

After making the replica antibiotic ointment was put in the eye and a pressure bandage applied for 48 hours. Generally, the epithelial wound created by the replica became re-epithelialised in this period. If a small epithelium defect remained, the eye was patched for another 24 hours.

The corneal replicas were examined by phase contrast and oblique illumination microscopy.[1 2] After dissolving the collodion membrane of the replica in acetone, the flat mounts of unstained diseased epithelial cells were again studied by these microscopic techniques. Subsequently, the cells were stained with haematoxylin-eosin, toluidine blue, or Giemsa stain. Some slides were first examined by a direct immunofluorescence technique, using fluorescein labelled antibodies against adenovirus, and then stained by one of the above methods.

Results

Punctate lesions did not reappear in the healed epithelium in nine patients after the replica was made. In three patients one to three punctate epithelial lesions developed, which disappeared within one week. There was no significant subepithelial opacification at the site of these lesions. In every patient punctate epithelial lesions in the untreated second eye persisted for 10 to 14 days, and marked subepithelial opacities developed at the site of epithelial lesions. These opacities did not disappear for several weeks or several months.

VIRUS CULTURE

Adenovirus was isolated from all eyes.

CYTOPATHOLOGY

Scrapings. Giemsa stained conjunctival scrapings showed a large number of lymphocytes and degenerated conjunctival epithelium cells with nuclear vacuolation. Inclusion bodies were not found in the material scraped from the conjunctiva.

Replicas. Phase contrast microscopy and

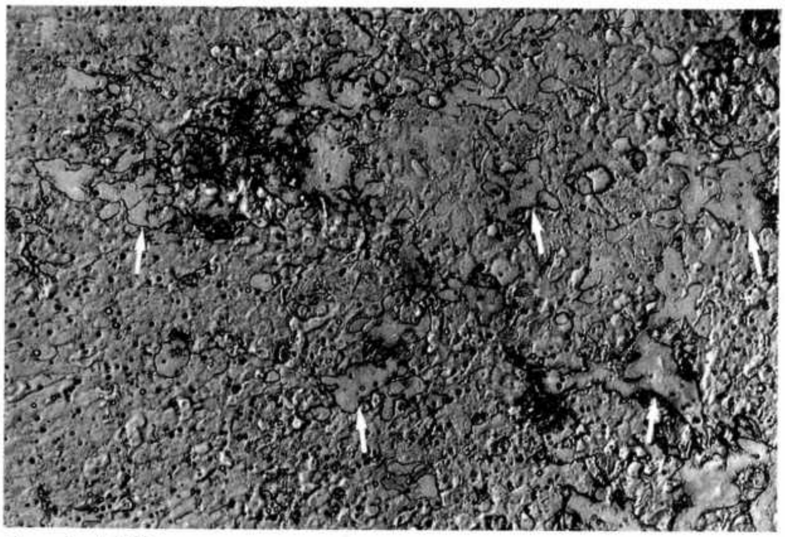


Figure 4 A diffuse epithelial lesion showing rounded, markedly swollen, epithelium cells. Some syncytia are indicated by arrows. Small round dots are artefacts. Oblique illumination microscopy. (× 150)

oblique illumination microscopy of the replicas demonstrated generalised oedema of the superficial epithelial cells without a change in their shape and size. Scattered among these cells were more swollen cells, either single or in groups of two to five cells, that had lost their normal configuration (Fig 2). Some of these cells had nuclear or cytoplasmic vacuoles or dark bodies by phases contrast microscopy.

Marked cellular changes were observed in the areas of punctate lesions. Some of the punctate lesions were focal in character (Fig 3), whereas others were more diffuse (Fig 4), showing cell alterations in wider areas. The boundaries of the lesions were not circumscribed, being constituted of cells with a moderate degree of swelling and structural deformation. The cells in the punctate lesions had become more or less rounded or globular and varied in shape and size. Some of them fused to form syncytia.

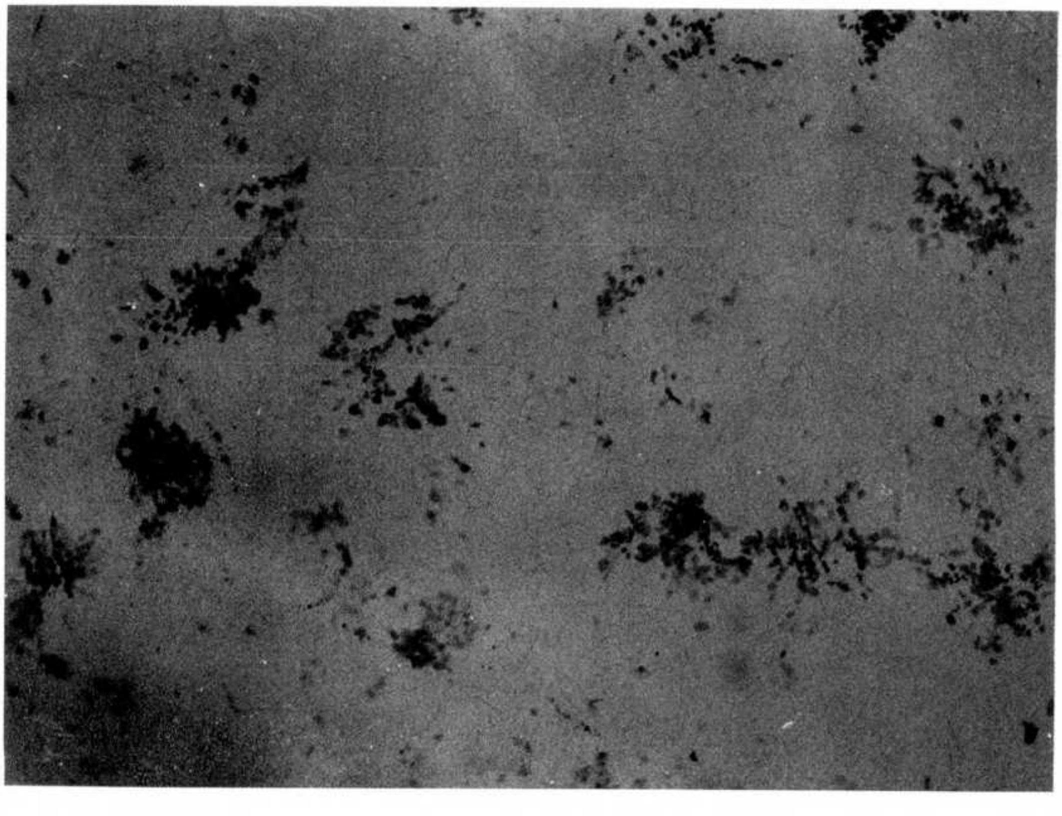
After dissolving the collodion membrane in acetone, flat mounts of diseased cells were first examined unstained and then again after staining. Most of the cells removed with the replica belonged to the areas of punctate lesions (Fig 5).

Cells from the punctate lesions showed stronger staining of their nuclei and cytoplasm than observed in normal epithelium cells, indicating a rise in their nucleoprotein content. In all replicas alterations in cell membrane were noted in many cells, which showed plicae on the cell surface by oblique illumination microscopy or dark lines by phase contrast microscopy (Fig 6). With the latter technique part of such a cell that had developed surface plicae appeared lighter than the rest of the cell. In stained slides this part of the cells was faintly coloured. These observations suggest that viral infection induces loss of cell contents, resulting in shrivelling of the cell walls. In fact, in many specimens empty envelopes of cell membranes devoid of any detectable cell contents were observed.

In other cells, especially at the periphery of the syncytia, oblique illumination microscopy showed small surface elevations, like pebbles projecting from the surface (Fig 6). By phase contrast microscopy of unstained cells, and light microscopy of stained slides, these surface elevations were found to be caused by cytoplasmic vacuoles. The nuclei of many cells also contained different sized vacuoles, whereas round dense bodies were present in other cells. Sometimes the dense bodies were located inside the nuclear vacuoles.

The intranuclear vacuoles appeared empty by haematoxylin-eosin stain (Fig 7), except when they contained round dense bodies, but toluidine blue and Giemsa staining showed the presence of light blue homogeneous material in them. This material did not show fluorescence by immunofluorescence technique. The intranuclear round dense bodies gave a strong positive immuno-

Figure 5 Flat mounts of diseased cells in punctate lesions after dissolving collodion membrane. (Haematoxylin-eosin, ×45)



FELLOWSHIP AVAILABLE IN GLAUCOMA

At the
UNIVERSITY OF
TORONTO
DEPARTMENT OF
OPHTHALMOLOGY
JULY 1991 TO JUNE 1992

Apply:
Chairman,
Department of Ophthalmology,
Toronto Western Hospital,
399 Bathurst Street,
Edith Cavell Wing,
Toronto, Ontario
M5T 2S8
Tel: 416/369-5799

** Personal interview required

I. G. S.

INTERNATIONAL GLAUCOMA SYMPOSIUM

Jerusalem
Israel
18–21 March, 1991

Symposium Topics:
Basic Research
New Diagnostic Tools
Medical Management
Lasers in Glaucoma
Surgery

Contact:
I.G.S. Organizers – Ofakim Ltd.,
5 Idelson Street, Tel Aviv, Israel 63324
Tel: 972-3-650514/7 Fax: 972-3-650513
Telex: 371254

UNIVERSITY OF LONDON

INSTITUTE OF OPHTHALMOLOGY

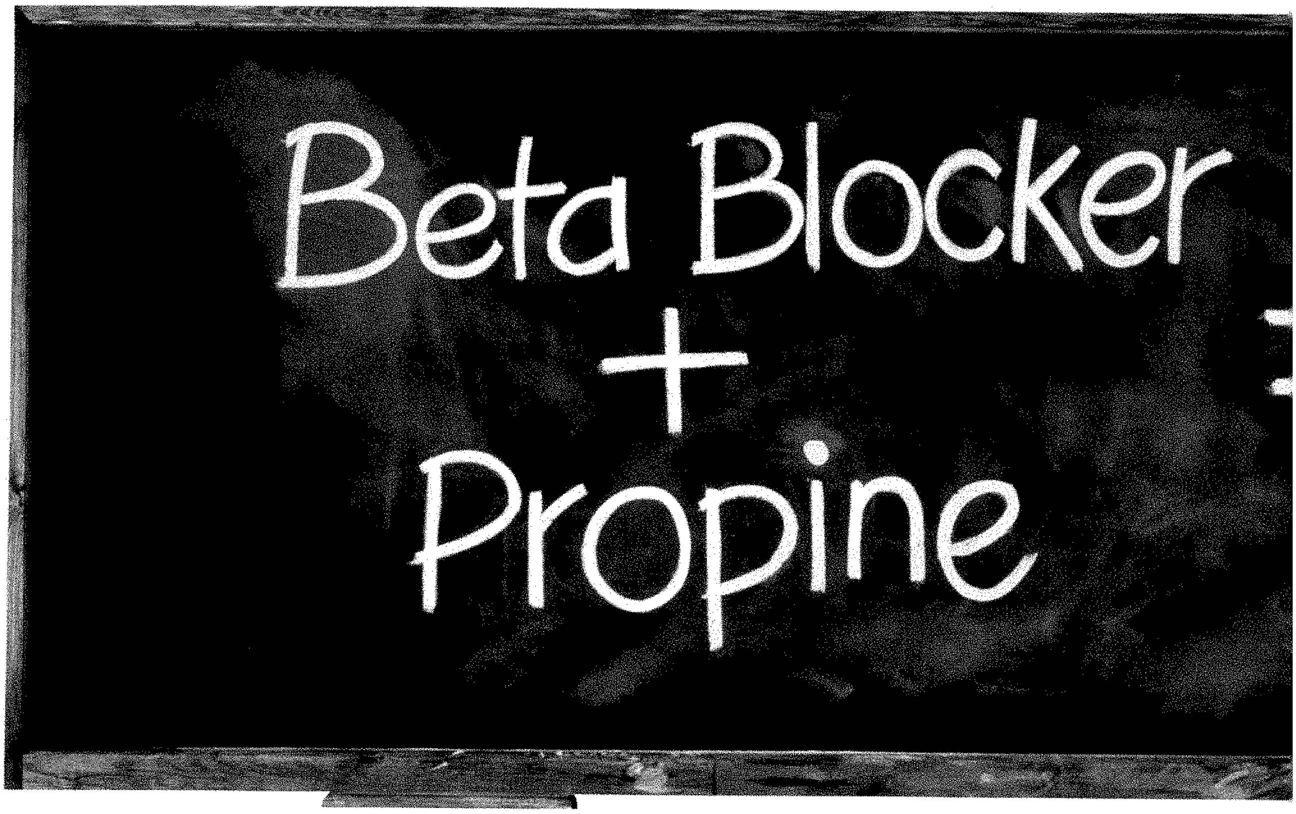
Associated with MOORFIELDS EYE HOSPITAL

The following Courses have been planned:

1990		
3rd-21st December	MCOphth/DO Modular Refresher Course	£550
	(one week module)	£200
1991		
14th-18th January	Paediatrics Course	£275
21st January-1st February	Final Fellowship Course	£400
11th-22nd February	MCOphth/DO Modular Refresher Course	£365
	(one week module)	£200
4th-8th March	GPs Course in Ophthalmology	£200
18th-22nd March	Lasers in Ophthalmology Course	£285
8th-10th April	Orthoptic Refresher Course	On application
15th-19th April	Optics and Refraction	£200
22nd-26th April	Basic Contact Lens Course	£290
2nd May	Diabetic Eye Day	£95
24th-28th June	Strabismus and Ocular Motility Course	£275

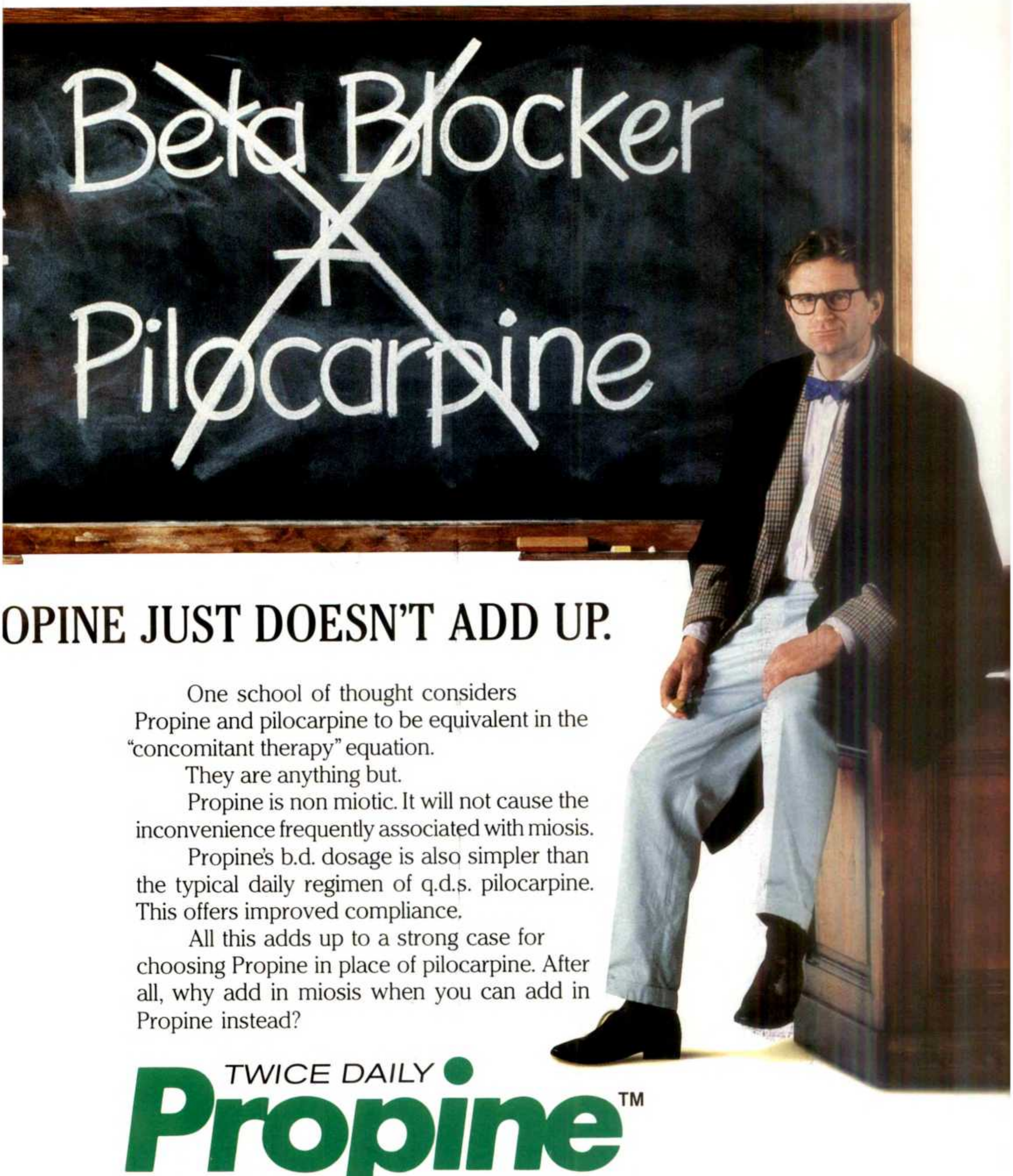
Applications for all courses should be made to the

Dean's Office, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT



EQUATING PILOCARPINE WI

PROPINE™ Prescribing Information
Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin
during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be
with caution in patients with narrow angles since dilation of the pupil may trigg
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adre
use in aphakic patients. Prompt reversal generally follows discontinuance of the
Macular oedema with dipivefrin does present as a possibility in the aphakic patient
product contains benzalkonium chloride and should not be used by patients conti
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachyc
arrhythmias and hypertension have been reported with ocular administratic



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY

Propine™

dipivefrin hydrochloride

A CLEAR CHOICE IN THE GLAUCOMA EQUATION

line, and may occur rarely with Propine therapy. Ocular: the most frequently ed side-effects are conjunctival injection, and burning and stinging on instillation. nd vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis, een reported occasionally. Adrenochrome deposits in the conjunctiva and cornea een associated rarely with use of dipivefrin. Follicular conjunctivitis has been ed during long term therapy with Propine. The condition is reversible upon discontin ce of the drug. **Pharmaceutical precautions** Store at room temperature. Discard used contents 28 days after opening the bottle. **Legal category** POM. **Package quantities** Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990.

TM denotes trademark

ALLERGAN PHARMACEUTICALS

Allergan Ltd., High Wycombe, Bucks HP12 3SH.

International Medical Course

Paediatric ophthalmology – surgical, medical and developmental aspects

16 - 25 May 1991, London

The care of children with visual and other eye problems, their rehabilitation if they are irretrievably blind, as well as the diagnostic and therapeutic aspects of management, have undergone radical changes in the last few years as a result of technological advances, changes in the understanding of visual development and its effect on the child, and a different approach by doctors to the way in which they help their patients. Most care of children with visual problems is initiated in the hospital but, in certain countries, the largest contribution is made outside the hospital. These changes in paediatric ophthalmology will be reflected in this course.

The course will include symposia on epidemiology, tumours, genetics, retina, neuro-ophthalmology, strabismus, cataract, glaucoma, plastic surgery, external diseases, cornea and lacrimal system, nystagmus, and the visually handicapped child. There will be special lectures on non-accidental injury and child abuse, incomitant strabismus, and dyslexia. A key-note lecture of retinopathy of prematurity will be given by Professor Alistair Fielder.

The course will be directed by **Mr David Taylor**, Consultant Ophthalmologist at the Hospital for Sick Children and Senior Lecturer at the Institute for Child Health, London, and **Mr Tony Moore**, Consultant Ophthalmologist, Addenbrooke's Hospital, Cambridge, and Associate Lecturer, University of Cambridge.

The course is designed for ophthalmologists who have, or wish to acquire, a particular interest in the needs of children but it is also intended for paediatricians who have an interest in ophthalmology.

There are vacancies for 35 participants.

Course fee: £1,255 inclusive of accommodation.

The working sessions will take place at the Institute of Child Health. Resident participants will be accommodated at a convenient hotel.

Further information and application forms are available from British Council Representatives overseas or from Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN

SPECIAL BMA MEMBERS EDITION

MIRROR OF MEDICINE
A HISTORY OF THE BMJ

P. W. J. BARTRIP

BMJ 1840-1990

The *BMJ*'s 150 year history has taken it from small beginnings in Worcester as the *Provincial Medical and Surgical Journal* to its current position as a major international medical journal. On the way there have been rows, editors' dismissals, and battles with the BMA and royal colleges as well as growing success and authority. In *Mirror of Medicine* the historian P W J Bartrip provides a shrewd and perceptive commentary on the *BMJ*'s progress, placing its history in the context of contemporary events and examining its treatment of many key themes in medical science and society.

352 pp., illus., Clarendon Press/BMJ,
September 1990

Price to BMA members only: UK £29; Abroad £33. Prices include packing and postage, by air speeded despatch abroad (air mail rates on application). AMEX, Access, Visa credit cards accepted.

Return address for orders: British Medical Journal, PO Box 295, London WC1H 9TE. (Also available in the BMJ/BMA bookshop in BMA House.)

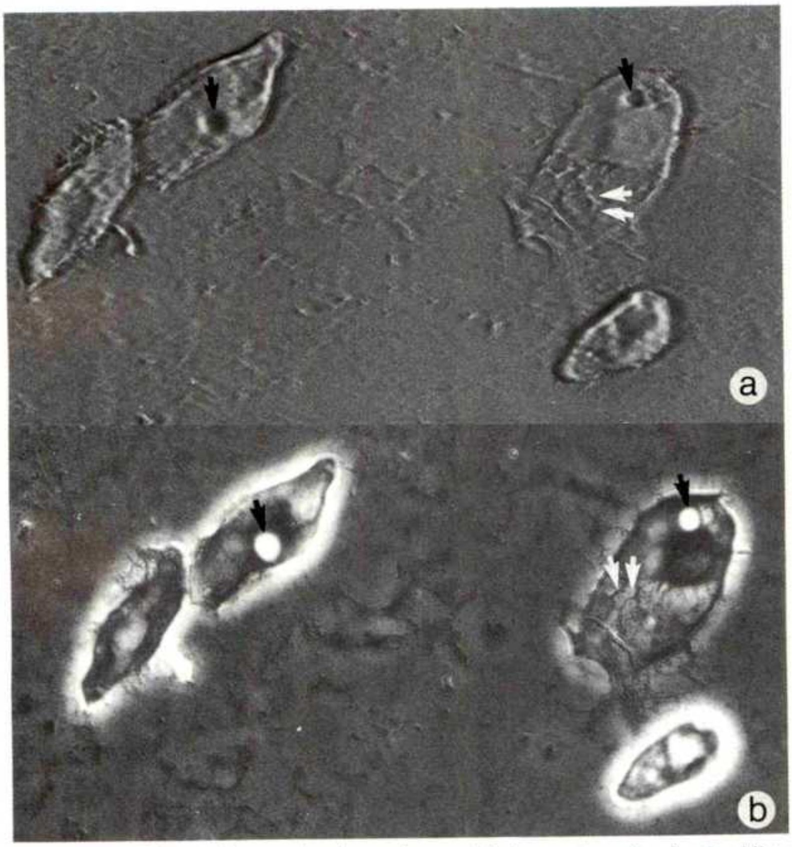


Figure 6 (a) Plicae (white arrow) and protruberances (black arrow) on cell surface by oblique illumination microscopy. (×720) (b) Plicae appear as dark lines (white arrows) and areas of surface protruberances as cytoplasmic vacuoles (black arrows) by phase contrast microscopy. (×720)

fluorescence reaction (Fig 8), and showed the characteristics of DNA by other staining techniques (Fig 9). It appears that the development of intranuclear vacuolar inclusions, containing homogeneous material, is probably an initial step in virus replication, and the formation of round dense bodies represents the development of adenovirus. The round dense bodies measured from 1 μm to 10 μm. In a few specimens round dense bodies were found in the extracellular spaces.

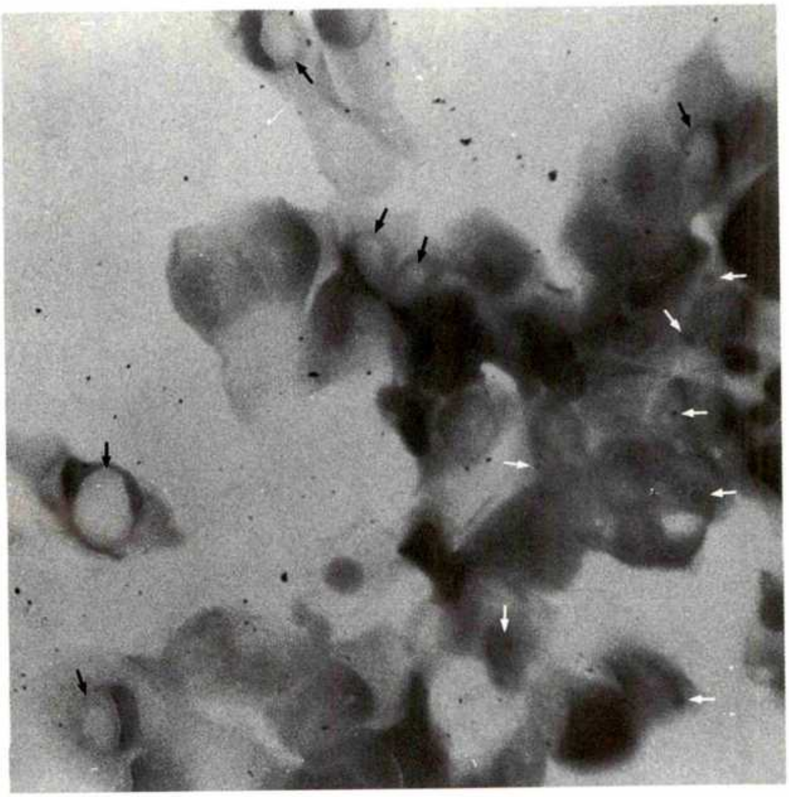


Figure 7 Intranuclear vacuolar inclusions (black arrows) present in many cells at the periphery of punctate lesion. Some round dense bodies (white arrows) are seen in the synctia and rounded epithelium cells. (Haematoxylin-eosin, ×720)

The swollen, globular cells in the punctate lesions also contained intranuclear vacuolar inclusions. However, round dense bodies were more frequently detected in these cells (Fig 9). Similarly, syncytia in the punctate lesions also contained round dense bodies. The central areas of some syncytia were necrosed, but the cell debris still contained a few dense round inclusion bodies.

Formation of pseudopodia-like processes from the syncytia was infrequently seen. When present, they were small, usually extending over two to five cell lengths. Leucocytes and ghost cells were not observed in our specimens.

Discussion

Duke-Elder[10] summarised the corneal histopathological changes in epidemic keratoconjunctivitis as degenerative alterations in the corneal epithelium and stroma, with infiltration of mononuclear cells at the site of epithelial lesions. Bowman's membrane is thinned or even disappears. Lund and Stefani[11] described the corneal focal lesions in epidemic keratoconjunctivitis as a collection of polymorphs and mononuclear cells.

The predominant mononuclear cell response in the Giemsa stained conjunctival scrapings in our patients is in agreement with the findings reported in the literature.[12]

Replica histology of adenovirus keratitis shows mild diffuse oedema of the corneal surface epithelium. The ribonucleoprotein content of the cells is increased, the increase probably induced by the synthesis and accumulation of virus specific proteins. Conversely, some cells show loss of cytoplasm and nuclei, with resulting formation of plicae on the cell surface of shrunken empty envelopes of cell membranes. More affected cells, showing moderate swelling and alterations in their shape and size, are found scattered among the less oedematous cells that still preserve their shape and size. Marked structural cellular changes are observed in the areas of punctate lesions. The cells vary in shape and size, having attained an oval or rounded form. They show a tendency to fuse together, resulting in syncytial formations. Parts of the syncytia undergo necrosis. Only rarely do small pseudopodia-like processes develop from the syncytia.

Although cell swelling, rounding, and syncytia formation also occur in herpes simplex virus keratitis,[1 6 8 9] there are distinct cytopathological dissimilarities between the punctate keratitis caused by adenovirus and by herpes simplex virus. The punctate lesions in herpetic keratitis are cytologically more focal in character, and they are always circumscribed by rows of elongated epithelial cells.[9] Round the branches of a dendritic figure the elongated cells are arranged in an arcuate pattern.[8 9] We have not observed the presence of elongated cells in any other type

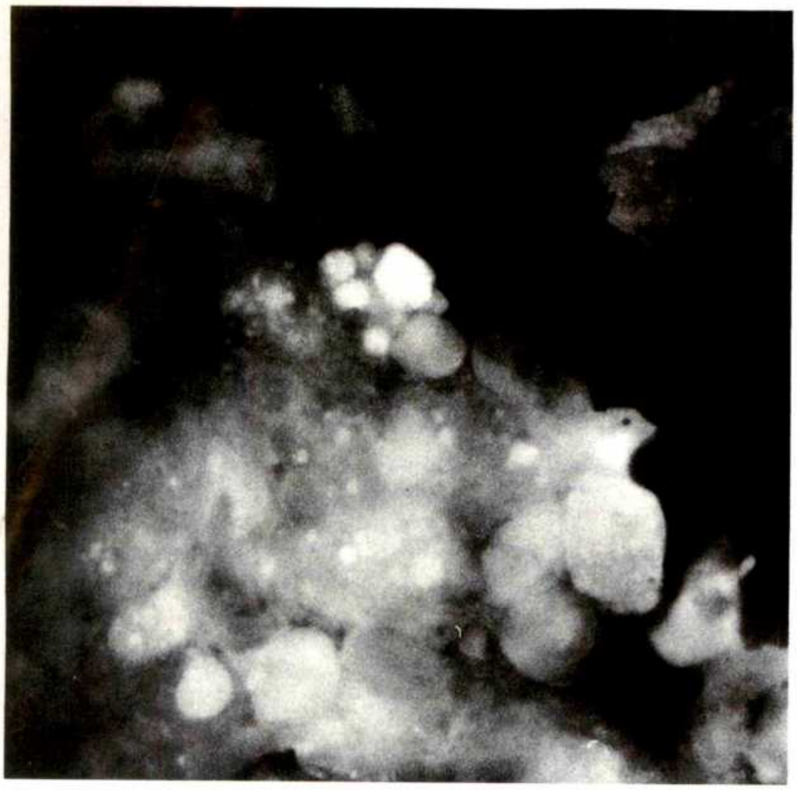


Figure 8 Round dense bodies exhibit a bright fluorescence by direct immunofluorescence technique to detect adenovirus. Note the variable size of dense bodies. (×720)

of epithelial keratitis. The syncytia in HSV infection are larger than in adenovirus keratitis. Equally, the pseudopodia-like processes are more numerous and larger in HSV punctate and dendritic keratitis, whereas in adenovirus keratitis they are rarely seen. The formation of plicae on the cell surface and loss of cell contents is, however, more frequent in adenovirus disease. Ghost cells, present in HSV infection,[6 8] were not found in adenovirus keratitis.

Two types of inclusions were detected in this study of adenovirus epithelial disease. The first type of intranuclear vacuolar inclusions containing homogeneous material develop commonly in the moderately altered cells. The homogeneous material in these inclusions is not antigenic in character as judged from the lack of fluorescence by the immunofluorescence technique.

The second type of inclusions are round dense bodies that develop in the homogeneous material of vacuolar inclusions. The dense bodies contain viral antigens, as shown by immunofluorescence technique and have the staining characteristics of DNA. The intranuclear vacuolar inclusions seem to be analogus to the intranuclear A-bodies of the herpes simplex virus replication cycle, wherein the replicating and maturing virus particles appear as A-granules.[15] However, the round dense bodies in adenovirus infection are not granular. They measure from 1 μm to 10 μm in size and are abundant in the moderately altered cells and syncytia. In the areas of necrosis they can be observed in the cell debris or even in extracellular positions.

An interesting finding in this study is the lack of any leucocytes in the superficial epithelium, even though abundant lymphocytes and some polymorphs are found in the conjunctival scrapings. Similarly leucocytes have not been observed in the replicas from herpetic dendritic ulcers or punctate keratitis.[8 9] Probably the lymphocytes and mononuclear cells penetrate into the deeper epithelial layers, and into the subepithelial stroma, owing to accumulation of viral antigens at these sites.[11 13 14]

After making the corneal replica, epithelial

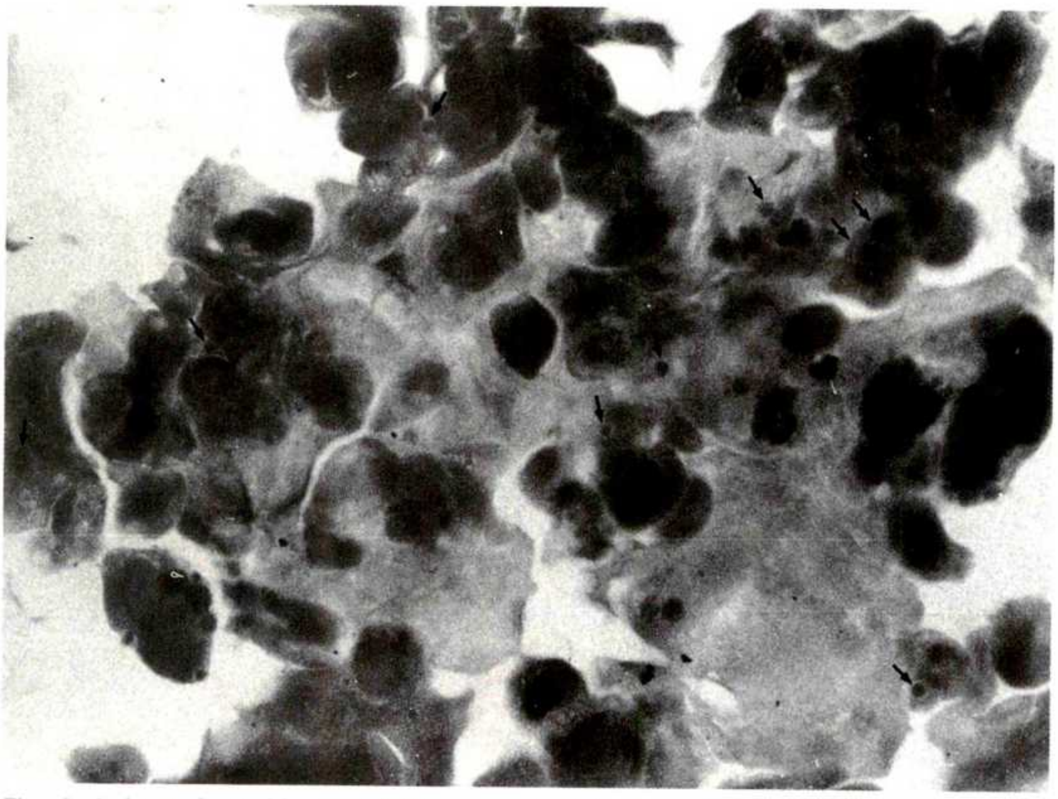


Figure 9 In the central parts of the punctate lesions the round dense bodies (some indicated by arrows) are abundant in the markedly altered cells. The staining pattern of inclusion bodies is that of nuclear DNA. (Haematoxylin-eosin, ×720)

lesions did not form in the regenerated epithelium in most cases, nor in these cases did subepithelial opacities develop. Since amyl acetate, used to dissolve collodion in the replica solution, penetrates into the superficial stroma[1-3] and kills the cells by fixation, the multiplying virus in the epithelium is probably destroyed by making the replica. Consequently the source of viral antigen which normally incites the mononuclear cell infiltration, resulting in development of subepithelial opacities on the basis of immune action, is eliminated.[13-15]

Making a corneal replica in adenovirus eye infection is not only a diagnostic aid: it may also be a therapeutic measure. The therapeutic effect of the replica technique in dendritic ulcers has been reported elsewhere.[16]

1 Maudgal PC. The epithelial response in keratitis sicca and keratitis herpetica. An experimental and clinical study. Doctoral thesis, University of Leuven, 1976. *Doc Ophthalmol* 1978; **45**: 223–327.
2 Missotten L, Maudgal PC. The corneal replica technique used to study the superficial corneal epithelium *in vivo*. *Am J Ophthalmol* 1977; **84**: 104–11.
3 Maudgal PC, Missotten L. Superficial keratitis. *Bull Soc Belge Ophtalmol* 1980; **187**: 2–6.
4 Maudgal PC, Missotten L. Histology and histochemistry of the normal superficial corneal epithelium of rabbit. *Graefes Arch Clin Exp Ophthalmol* 1978; **205**: 167–74.
5 Maudgal PC, Missotten L. Development of disseminating inclusion bodies in primary experimental herpes simplex keratitis. *Bull Soc Belge Ophtalmol* 1977; **179**: 25–36.
6 Maudgal PC, Missotten L. Histopathology and histochemistry of the superficial corneal epithelium in experimental herpes simplex keratitis. *Graefes Arch Clin Exp Ophthalmol* 1979; **209**: 239–48.
7 Love R, Wildy P. Cytochemical studies of the nucleoproteins of HeLa cells infected with herpes virus. *J Cell Biol* 1963; **17**: 237–54.
8 Maudgal PC, Missotten L. Histopathology of human superficial herpes simplex keratitis. *Br J Ophthalmol* 1978; **62**: 46–52.
9 Maudgal PC, Missotten L. Histopathological study of the human herpes simplex dendritic and punctate keratitis by replica technique. *Doc Ophthalmol Proc Ser* 1979; **20**: 211–9.
10 Duke-Elder S. Diseases of the outer eye. *System of ophthalmology*. London: Kimpton, 1965: **8**: (1): 352–8.
11 Lund OE, Stefani FH. Corneal histology after EKC. *Arch Ophthalmol* 1978; **96**: 2085–8.
12 Vastine DW, Wilmer BI. Adenoviridae. In: Darrell RW, ed. *Viral diseases of the eye*. Philadelphia: Lea and Febiger, 1985: 131–46.
13 Dawson CR, Hanna L, Togni B. Adenovirus type 8 infections in the USA. IV. *Arch Ophthalmol* 1972; **87**: 258–68.
14 Periera HG. Persistent infection by adenoviruses. *J Clin Pathol* 1972; **25** (suppl 6): 39–42.
15 Jones BR. The clinical features of viral keratitis and a concept of their pathogenesis. *Proc R Soc Med* 1958; **51**: 13–20.
16 Maudgal PC, Van Deuren H, Missotten L. Therapeutic effect of corneal replica in herpetic keratitis. *Bull Soc Belge Ophtalmol* 1979; **185**: 39–46.

British Journal of Ophthalmology, 1990, 74, 676–680

Pupillary responses in amblyopia

Alison Y Firth

Abstract

Relative afferent pupillary defects (RAPD) were detected in 32·3% of patients with amblyopia by a modification of the swinging flashlight test and the synoptophore. After consideration of various clinical investigations the significant factors identified in patients showing a RAPD were: anisometropia, early age of onset where strabismus was present, level of visual acuity following treatment, longer period of occlusion therapy. These points bear similarities to the results of pattern electroretinograms (PERG) in amblyopes, and the possibility of the causative defect being at ganglion cell level is discussed. The effect of occlusion treatment cannot be predicted from the presence or absence of a RAPD.

An afferent or relative afferent pupillary defect has been reported to be present in between 9% and 93% of amblyopes.[1-6] The main criticism of these findings is that poor fixation in the amblyopic eye may result in the light stimulus striking different retinal areas.[7]

Routine orthoptic examination does not include a test capable of detecting small afferent or relative afferent pupillary defects. When attempting to assess the latter, the swinging flashlight test[8,9] is used, but this has drawbacks for the examination of children. The child will often look at the light causing constriction of the pupil due to the near reflex, which obscures the response to light,[10] or the reaction may be blocked in excitable children.[11] In addition other disadvantages to the test include: confusion due to hippus[7] (one pupil being observed on the upswing and the other on the downswing), presence of anisocoria,[9] and the danger of using too bright a light, as an after image can keep the pupils small and so prevent the pupillary escape.[11,12]

Pupillomotor changes have also been reported in suppression.[13]

The implication of the presence of a relative afferent pupillary defect in diagnosis and management of amblyopia has not been fully determined. The purpose of this study was to discover factors common to amblyopes who display a defect with a view to ascertaining whether assessment of the pupillary response is of clinical value during the treatment of amblyopia.

Welsh School of Orthoptics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW
A Y Firth

Correspondence to:
Alison Y Firth.

Accepted for publication
7 June 1990

Methods and patients

To observe any asymmetry in pupillary response the synoptophore was used with modification of the bright light source normally used for the production of after images. The light intensity was reduced by fitting neutral density filters (NDF) of 0·4 log units into the same rubber holder as each eye piece lens. The after image light was then alternatively switched from one eye to the other, giving a period of stimulation of 1 to 2 seconds, and the initial pupillary constriction was observed. The light was then left in front of each eye for a count of 3 and the pupillary escape noted.

If a pupillary defect was observed, a neutral density filter was placed in the arm of the synoptophore in front of the eye without the defect. In practice it was not found possible to quantify the defect to within 0·1 log unit as has previously been reported,[5] but merely to confirm its presence. Where no defect was initially apparent, a 0·3 log unit NDF was placed in either arm in turn to produce a difference in response. In some cases this revealed a subtle defect, as the pupillary response was still present but to a lesser extent in one eye while completely absent in the other. During the examination refractive correction was worn, the interpupillary distance corrected, and the tubes set at the objective angle of deviation by rotating each arm equally, thus ensuring similar stimulation in either eye. The patient fixed simultaneous macular perception slides throughout.

Where possible this test was performed blind, but casual observation – as in cases of obvious anisometropia or strabismus, wearing of occlusion, comment on suppression – meant that the amblyopic eye was known to the examiner in some cases.

After the assessment of the pupillary reaction on the synoptophore the density of any suppression present was measured at the objective angle by dimming the rheostat in front of the non-suppressing eye until the 'suppressed' image could be seen and the rheostat number noted. The subjective and objective angles were compared to elicit the type of retinal correspondence.

Visual acuity was assessed (with the patient wearing refractive correction) by a linear test (Snellen or Snellen with key card). Some patients had their acuity tested with single optotypes (Sheridan Gardiner), fixation by the Visuscope and contrast sensitivity by the American Optical System (which is based on Arden's gratings). The size of pupils was measured, as any anisocoria or more than 2 mm could make the testing of pupillary responses inaccurate.[9]

Further details were taken from the hospital records. These included: age at date of test, type of amblyopia, age at onset of strabismus, visual acuity prior to occlusion therapy (and test used), age at first occlusion, types of occlusion therapy undergone, continuity of occlusion, best previous visual acuity (if higher than on day of testing), refractive correction, and fundus examination. When any lesion of the fundus or media was present the patient was excluded.

Since the study was of necessity conducted during normal clinical sessions, the selection of patients was haphazard. They were examined during their routine orthoptic examinations. Initially only patients with amblyopia were examined, but later all patients examined with no prior knowledge of whether or not amblyopia was present. No attempt was made to examine patients under the age of 3 years. Nine children were followed up through occlusion therapy.

A group of 25 children from a local junior school were used as controls.

Results

Seventy six patients were examined with ages ranging from 3 years 2 months to 13 years 10 months. Sixty five had amblyopia, this being defined as any difference in linear visual acuity. The type of amblyopia is shown in Table 1.

Of the patients with equal visual acuity four had previously had strabismic amblyopia which had responded to treatment, five had intermittent or alternating deviations, and two had equal but reduced visual acuity due to ametropic amblyopia.

The pupillary responses in 72% of patients were examined blind.

Of the 65 amblyopic patients 21 had a relative afferent pupillary defect in their amblyopic eye and two in their non-amblyopic eye. Of 25 controls tested a subtle defect was found in one child.

Contraction anisocoria is estimated to occur to an extent which is clinically visible in 5% of the population.[11] This may explain the finding of a defect in the control and non-amblyopic eyes. However, it could have been observer error. The two patients with the defect in their non amblyopic eye were excluded from further consideration.

The type of amblyopia of the remaining 63 patients was first considered (Fig 1). For statistical evaluation the idiopathic group was excluded because of the low number. By means of the likelihood ratio criterion the type of amblyopia was shown to be significant at the $p<0{\cdot}02$ level, and further grouping of patients into those with or without anisometropia (Table 2) and those with or without strabismus (Table 3) showed only the difference in the former group to be significant ($p<0{\cdot}01$). The actual amount of anisometropia, however, did not prove to be significant.

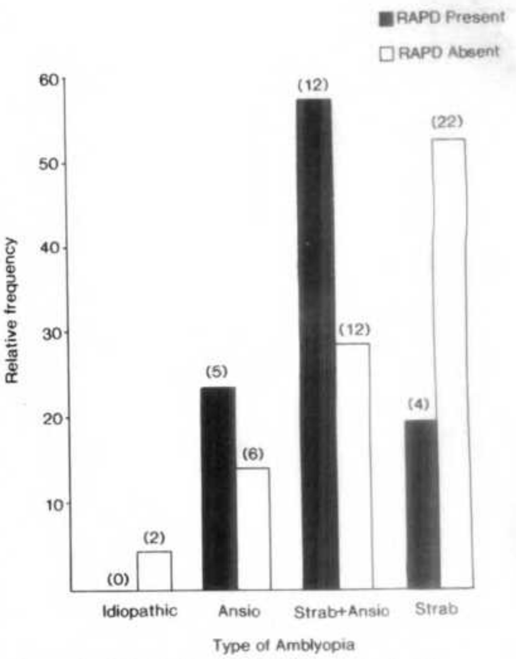


Figure 1 Relative frequencies of different types of amblyopia: idiopathic, anisometropic (aniso), combination of strabismic and anisometropic (strab + aniso) and strabismic (strab) in patients with (shaded) and without (unshaded) a relative afferent pupilary defect (RAPD). Actual patient numbers shown in brackets.

An accurate age at onset in those with strabismus was given in 35 patients. The Mann-Whitney U test showed the age at onset to be at a significantly younger age in those with a relative afferent pupillary defect ($p=0{\cdot}0294$). However, as eight out of the nine patients with a pupillary defect also had anisometropia and only seven out of 26 without a defect were anisometropic, it was considered that this may have caused a bias.

Unfortunately the numbers were too small to analyse in the pure strabismic amblyopes, but in a comparison of patients with anisometropia and strabismus (Fig 2) the age at onset of the strabismus was found by the Mann-Whitney U test to be significant at the $p<0{\cdot}05$ level.

Various factors concerning occlusion were considered: (*a*) age at first occlusion; (*b*) the delay from onset of strabismus to start of occlusion; (*c*) type and continuity (*d*) period of occlusion; and (*e*) time lapse from the last occlusion to the date of testing. Of these, the period of occlusion (Fig 3) was the only significant

Table 2 Presence or absence of relative afferent pupillary defect (RAPD) in amblyopia involving anisometropia and amblyopia without anisometropia. Statistical evaluation given

	Type of amblyopia		
	Aniso and Strab+Aniso	*Pure strab*	*Total*
RAPD present	17	4	21
RAPD absent	18	22	40
Total	35	26	61

$X_L^2=7{\cdot}7297883$, df=1, $p<0{\cdot}01$ (2 tailed).

Table 3 Presence or absence of relative afferent pupillary defect (RAPD) in amblyopia involving strabismus and amblyopia without strabismus. Statistical evaluation given

	Type of amblyopia		
	Pure Aniso	*Aniso+strab and strab*	*Total*
RAPD present	5	16	21
RAPD absent	6	34	40
Total	11	50	61

$X_L^2=0{\cdot}7011637$, df=1, not significant

Table 1 Number of patients with each type of amblyopia in the presence or absence of a relative afferent pupillary defect (RAPD)

	Type of amblyopia				
	Idiopathic	*Aniso*	*Stab+Aniso*	*Strab*	*Total*
RAPD present	0	5	12	4	21
RAPD absent	2	6	12	22	42
Total	2	11	24	26	63

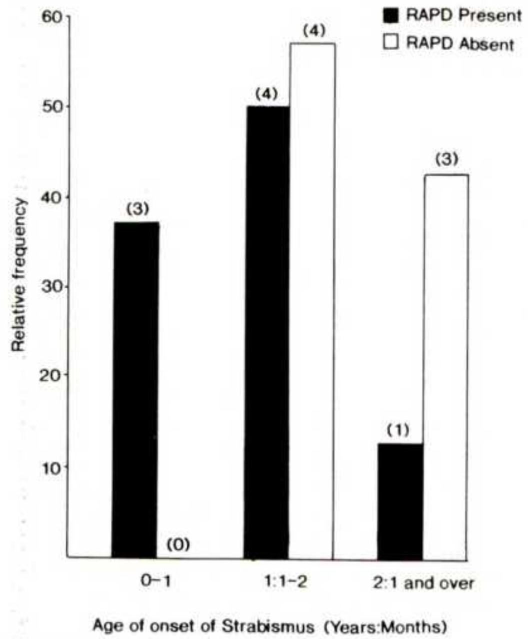


Figure 2 Relative frequencies of the age of onset of strabismus in anisometropic patients with (shaded) and without (unshaded) a relative afferent pupillary defect (RAPD). Actual patient numbers shown in brackets.

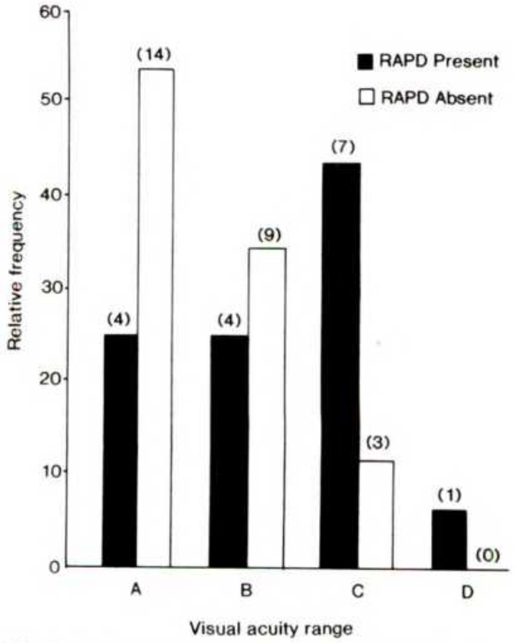


Figure 4 Relative frequencies of the range of visual acuity of the amblyopic eye in patients who had undergone occlusion therapy with (shaded) and without (unshaded) a relative afferent pupillary defect (RAPD). A: up to 6/9; B: 6/10·5 to 6/18; C: 6/21 to 6/36; D: 6/48 and below. Actual patient numbers shown in brackets.

factor (p=0·0188). This suggests that in patients with a relative afferent pupillary defect it was either more difficult to gain an improvement or their acuity was more difficult to stabilise.

Statistical examination of the results of retinal correspondence, state of fixation, density of suppression, and contrast sensitivity showed no significant differences.

Different aspects of visual acuity were examined including: (*a*) linear acuity in patients who had undergone occlusion and those who had not; (*b*) presence of crowding; and (*c*) the incidence of visual acuity being at less than its best level. The only significant factor (p=0·0054) found was the level of visual acuity in patients who had undergone occlusion (Fig 4). Visual acuity was lower in those with a relative afferent pupillary defect. (The level of visual acuity was not significant prior to occlusion.)

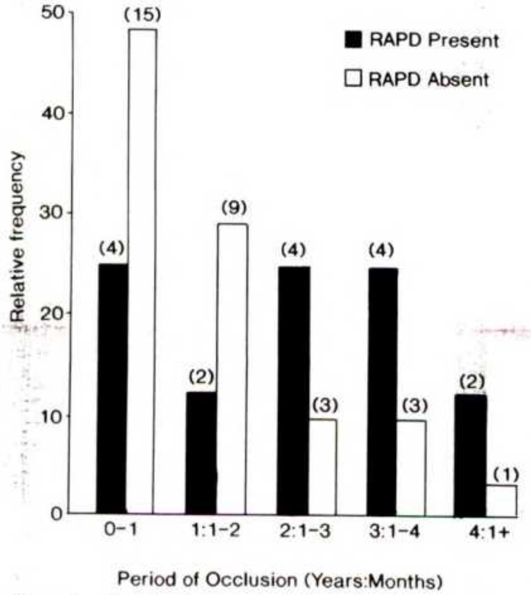


Figure 3 Relative frequencies of the period of occlusion in patients with (shaded) and without (unshaded) a relative afferent pupillary defect (RAPD). Actual patient numbers shown in brackets.

Finally nine patients were followed up through treatment. Three had a relative afferent pupillary defect and had not had prior treatment. In two of these the defect disappeared, but in the third it persisted. Three of the nine had a defect but had already undergone some occlusion; in one the defect disappeared, and three showed no relative afferent pupillary defect and had not been occluded. In one of these a defect was never seen, but in the other two a defect appeared in the non-amblyopic eye which disappeared after occlusion was stopped.

Discussion

AFFERENT OR EFFERENT?

The present study, owing to the method of testing used, does not answer this question. However, the defect has been shown to occur only on stimulation of the central area of the retina and not the periphery, and not by stimulation with blue light.[14] Further, there is no delay in the consensual reaction[15] on stimulation of the non-amblyopic eye.

CAUSE

A defect prior to the lateral geniculate nucleus (LGN) is the most likely explanation, though other reasons may be considered. Inhibition either of the retina or the Edinger-Westphal nucleus may occur. Evidence for the presence of centrifugal fibres in the optic nerve has been published,[16 17] but doubt is now expressed about their presence. The central nervous system (CNS) has been shown to be capable of inhibition at the level of the Edinger-Westphal nucleus.[18]

This may play a part in pupillomotor changes in suppression, but in the testing of amblyopes the stimulated eye is observed, and no effort of a psychosensory nature to prevent the reaction is being made.

A similar sized RAPD has been reported in optic tract hemianopia,[19] where midnasal pallor of the optic disc in the ipsilateral eye is present. Experimentally, cutting of the optic tract (in monkeys) produces a similar afferent pupillary defect and pattern of atrophy.[20] It is extremely unlikely that postchiasmal changes in amblyopia would cause such a pupillary defect in the presence of a normal disc appearance.

If the retina is considered at the site for the cause, then again several suggestions may be made. Retinal haemorrhages at birth could cause an undetectable retinal defect.[21] However, from a series of babies followed up to an age at which visual acuity could be measured, these haemorrhages did not appear to have any detrimental effect on the normal development of vision.[22]

Malorientation of the retinal receptors has been suggested as a cause of organic amblyopia;[23, 24] this would result in less light being absorbed. However, the findings of malorientation of the receptors is disputed,[25] and normal cone electroretinogram recordings, suggestive of normal preganglionic cell function, have been reported in amblyopia.[26]

Pattern electroretinograms (PERG), which reflect the integrity of the ganglion cell layer, are abnormal in amblyopia,[27–30] though this has not been confirmed by every study.[31, 32] If the cause of the abnormal pupillary response lies at ganglion cell level, then some similarities in the type of patient having a RAPD and showing an abnormal PERG may be expected. Where an analysis of the PERG response has been related to different categories of patients and treatment,[29] it was found that the greatest defects occurred in anisometropes and those patients who did not respond well to treatment. Furthermore, reduction in the amplitude of the PERG in the occluded, non-amblyopic eye, occurred, which reversed with the cessation of treatment.[29]

X and *Y* ganglion cell function has been shown to be abnormal in cats raised with strabismus,[33, 34] though again there is dispute.[35] Often the strabismus (or anisometropia) is produced in the animal at around 3 to 4 weeks of age,[33–38] though sometimes this has varied.[39, 40] The lower spatial frequencies (in the cat) are unaffected where strabismus is produced after eight weeks,[39] and in infants the low frequency end of the contrast sensitivity function (CSF) curve does seem to develop to an adult-like shape earlier than the high frequency end.[41]

The Y and W cells are probably responsible for the detection of low to medium spatial frequencies.[42] It has been suggested that the luminance detectors originally identified[43] which showed a regularly increasing frequency of discharge with an increase in adaptation level are W cells.[44] Thus it is plausible that early-onset strabismics are more likely to show changes which result in a RAPD. However, the case for anisometropes is less clear, as it cannot be assumed that the difference in refractive error is present at birth. There is no mention of anisometropia in newborn babies screened with photorefraction,[45–47] and the incidence in 6- to 9-month olds appears far less than in school age children.[48, 49] In fact between the ages of 1 and 3½ years anisometropia may either develop or resolve.[50] Anisohypermetropia has been produced by radial keratotomy in kittens,[51] and axial length changes have compensated for this provided accommodative function is intact and there is normal visual experience.

Accommodative function may be abnormal in anisometropic amblyopia. Although defective accommodation has been reported in amblyopia,[52] the consensual response when the non-amblyopic eye is stimulated is normal.[53] Unsteady fixation, perceptual difficulties, or lack of foveal function may be the cause of this apparent defect.[54–56]

If accommodative function is normal, then a lack of normal visual experience in one eye may be the cause of the lack of emmetropisation and the resultant anisometropia. If the cause of such is an undetectable defect in the retina (post-receptor level or ganglionic level), this may be the explanation for the differences in CSF between anisometropic and strabismic amblyopes[57–59] and be the cause of the RAPD and abnormal PERG responses.

TREATMENT

During occlusion there may be some reversibility of the RAPD, or it may be that a defect is being produced in the occluded eye, thus masking that in the amblyopic eye. As mentioned above,[29] the PERG reduces in the occluded eye and disruption of the orientation of retinal receptors occurs.[60] Further study is needed to quantify the pupillary reactions of each eye to determine the answer to this question. It has been reported[3] that increased latencies of contraction become more normal with treatment. As the level of visual acuity prior to occlusion therapy is not significant to the presence of a RAPD, this test cannot be used as an indicator of the outcome of occlusion therapy in amblyopia.

I would like to thank the consultant ophthalmologists at the University Hospital of Wales for allowing me to use their patients Thanks also go to the headmaster and children of Tirphil Primary School; Mr A K W Henn for translations; the Department of Medical Illustrations; Dr T J Peters for advice and help with the statistics; Miss J V Plenty for helpful comments on the paper; my colleagues at work; and Dr J M Woodhouse for overseeing the project.

1 Dolenek A Bietrag zur pupillographie. *Ophthalmologica* 1960; 139: 77–83.
2 Kruger KE. Pupillenstorungen und amblyopie. *Ber Dutsch Ophthalmol Ges* 1960; 63: 275–8.
3 Dolenek A, Kristek A, Nemec J, Komenda S. Uber Veranderunden der Pupillenreaktion nach erfolgreicher Amblyopiebehandlung. *Klin Monatsbl Augenheilkd* 1962; 141: 353–7
4 Greenwald MJ, Folk ER. Afferent pupillary defects in amblyopia *J Pediatr Ophthalmol Strabismus* 1983, 20: 63–7.
5 Portnoy JZ, Thompson HS, Lennarson L, Corbett JJ Pupillary defects in amblyopia. *Am J Ophthalmol* 1983, 96: 609–14
6 Cremers H. Pupillary abnormalities in amblyopia. *Aust Orthopt J* 1986; 23: 47 (abstr).
7 Thompson HS. Afferent pupillary defects (Pupillary findings associated with defects of the afferent arm of the pupillary light reflex arc). *Am J Ophthalmol* 1966, 62: 860–73
8 Levatin P. Pupillary escape in disease of the retina or optic nerve *Arch Ophthalmol* 1959; 62: 768–79.
9 Thompson HS, Corbett JJ, Cox TA. How to measure the relative afferent pupillary defect. *Surv Ophthalmol* 1981; 26: 39–42
10 Cox TA Pupillary testing using the direct ophthalmolscope *Am J Ophthalmol* 1988; 105: 427–8

11 Thompson HS. Pupillary signs in the diagnosis of optic nerve disease. *Trans Ophthalmol Soc UK* 1976; 96: 377–81

12 Borchett M, Sadun AA. Bright light stimuli as a mask of relative afferent pupillary defect *Am J Ophthalmol* 1988, 106: 98–9

13 Brenner RL, Charles ST, Flynn JT. Pupillary responses in rivalry and amblyopia *Arch Ophthalmol* 1969; 82: 23–9.

14 Trimarchi F, Casali G, Franchini F, Gilardi E. Pupillographic responses in patients with untreated amblyopia. In: Moore S, Mein J, Stockbridge L, eds. *Orthoptics. past, present, future Trans 3rd Int Orthopt Cong* 1976; 69–73.

15 Kase M, Nagata R, Yoshida A, Hanada I Pupillary light reflex in amblyopia *Invest Ophthalmol Vis Sci* 1984; 25: 467–71.

16 Jacobson JH, Gestring GF Spontaneous retinal electrical potential. *Arch Ophthalmol* 1959; 62: 599–604.

17 Wolter JR, Knoblich RR Pathway of centrifugal fibres in the human optic nerve, chiasm, and tract. *Br J Ophthalmol* 1965; 49: 246–50.

18 Lowenstein O, Loewenfeld IE. The pupil. In: *Davson H ed The Eye* New York and London Academic Press. 1962; iii: 246.

19 Bell RA, Thompson HS Relative afferent pupillary defect in optic tract hemianopias. *Am J Ophthalmol* 1978; 85: 538–40.

20 O'Connor PS, Kasdon D, Tredici TJ, Ivan DJ. The Marcus Gunn pupil in experimental tract lesions *Ophthalmology* 1982, 89: 160–4

21 Burian HM, Noorden GK von. *Binocular vision and ocular motility*. St Louis: Mosby, 1974, 222.

22 Noorden GK von, Khodadoust A. Retinal hemorrhage in newborns and organic amblyopia. *Arch Ophthalmol* 1973; 89: 91–3

23 Enoch JM. Receptor amblyopia *Am J Ophthalmol* 1959, 48: 262–73.

24 Enoch JM. Further studies on the relationship between amblyopia and the Stiles-Crawford effect. *Am J Optom Physiol Opt* 1959; 36: 111–28.

25 Bedell HE Central and peripheral retinal photoreceptor orientation in amblyopic eyes as assessed by the psychophysical Stiles-Crawford function *Invest Ophthalmol Vis Sci* 1980; 19: 49–59

26 Jacobson SG, Sandberg MA, Effron MH, Berson EL. Foveal cone electroretinograms in strabismic amblyopia. Comparison with juvenile macular degeneration, macular scars and optic atrophy *Trans Ophthalmol Soc UK* 1979; 99: 353–6.

27 Sokol S, Nadler D. Simultaneous electroretinograms and visually evoked potentials from adult amblyopes in response to a pattern stimulus. *Invest Ophthalmol Vis Sci* 1979; 18: 848–55.

28 Wanger P, Persson HE. Oscillatory potentials, flash and pattern-reversal electroretinograms in amblyopia *Acta Ophthalmol (kbh)* 1984; 62: 643–50

29 Arden GB, Wooding SL Pattern ERG in amblyopia. *Invest Ophthalmol Vis Sci* 1985) 26; 88–96.

30 Arden GB Pattern evoked ERGs in amblyopia Paper presented at British Orthoptic Society Annual Scientific Conference, Glasgow, 1988

31 Hess RF, Baker CL, Verhoeve JN, Keesey UT, France TD. The pattern evoked electroretinogram: its variability in normals and its relationship to amblyopia. *Invest Ophthalmol Vis Sci* 1985; 26: 1610–23.

32 Gottlob I, Welge-Lussen L. Normal pattern electroretinograms in amblyopia. *Invest Ophthalmol Vis Sci* 1987; 28: 187–91.

33 Ikeda H, Tremain KE Amblyopia occurs in retinal ganglion cells in cats reared with convergent squint without alternating fixation *Exp Brain Res* 1979; 35: 559–82.

34 Chino YM, Shansky MS, Hamasaki DI. Development of receptive field properties of retinal ganglion cells in kittens raised with a convergent squint. *Exp Brain Res* 1980; 39: 313–20

35 Cleland BG, Crewther DP, Crewther SG, Mitchell DE Normality of spatial resolution of retinal ganglion cells in cats with strabismic amblyopia *J Physiol (Lond)* 1982; 326: 235–49.

36 Chino YM, Shanksky MS, Jankowski WL, Banser FA. The effects of rearing kittens with convergent strabismus on receptive-field properties in striate cortex neurones. *J Neurophysiol* 1983; 50: 265–86.

37 Eggers HM, Blakemore C. Physiological basis of anisometropic amblyopia. *Science* 1978; 201: 264–7.

38 Ikeda H, Tremain KE. Amblyopia resulting from penalisation: neurophysiological studies of kittens reared with atropinisation of one or both eyes *Br J Ophthalmol* 1978; 62: 21–8

39 Jacobson SG, Ikeda H. Behavioural studies of spatial vision in cats reared with convergent squint: is amblyopia due to arrest of development? *Exp Brain Res* 1979; 34: 11–26.

40 Ikeda H, Tremain KE, Einon G Loss of spatial resolution of lateral geniculate neurones in kittens raised with convergent squint produced at different stages of development. *Exp Brain Res* 1978; 31: 207–20.

41 Atkinson J, Braddick O. Assessment of vision in infants. Applications to amblyopia. *Trans Ophthalmol Soc UK* 1979; 99: 338–43.

42 Kulikowski JJ, Tolhurst DJ. Psychophysical evidence for sustained and transient detectors in human vision. *J Physiol (Lond)* 1973; 232: 149–62.

43 Barlow BHB, Levick WR Changes in the maintained discharge with adaptation level in the cat retina. *J Physiol (Lond)* 1969; 202: 699–718.

44 Stone J, Fukuda Y. Properties of cat retinal ganglion cells: a comparison of W cells with X and Y cells. *J Neurophysiol* 1974; 37: 722–48.

45 Mohindra I, Held R, Gwiazda J, Brill S. Astigmatism in infants. *Science* 1978; 202: 329–31.

46 Howland HC, Atkinson J, Braddick O, French J. Infant astigmatism measured by photorefraction. *Science* 1978; 202: 331–33

47 Kaakinen K, Ranta-Kemppainen L. Screening of infants for strabismus and refractive errors with two flash photorefraction with and without cycloplegia. *Acta Ophthalmol (kbh)* 1986; 64: 578–82.

48 Atkinson J, Braddick OJ, Durden K, Watson PG, Atkinson S. Screening for refractive errors in 6–9 month old inflants by photorefraction. *Br J Ophthalmol* 1984; 68: 105–12.

49 Vries JD. Anisometropia in children: analysis of a hospital population. *Br J Ophthalmol* 1985; 69: 504–7.

50 Ingram RM, Traynar MJ, Walker C, Wilson JM Screening for refractive errors at age one year: a pilot study. *Br J Ophthalmol* 1979; 63: 243–50.

51 Hendrickson P, Rosenblum W Accommodation demand and deprivation in kitten ocular development *Invest Ophthalmol Vis Sci* 1985; 26: 343–9.

52 Abraham SV. Accommodation in the amblyopic eye. *Am J Ophthalmol* 1961; 52: 197–200

53 Hokoda SC, Ciuffreda KJ. Measurement of accommodative amplitude in amblyopia. *Ophthalmic Physiol Opt* 1982; 2: 205–12.

54 Kirschen DG, Kendall JH, Riesen KS An evaluation of the accommodative response in amblyopic eyes. *Am J Optom Physiol Opt* 1981; 58: 597–602

55 Wood ICJ, Tomlinson A. The accommodative response in amblyopia. *Am J Optom Physiol Opt* 1975; 52: 243–7.

56 Otto J, Safra D. Methods and results of quantitative determination of accommodation in amblyopia and strabismus. In Moore S, Mein J, Stockbridge L, eds. *Orthoptics. past, present, future. Trans 3rd Int Orthopt Cong* 1976; 45–58.

57 Hess RF, Howell ER. The luminance-dependent nature of the visual abnormality in strabismic amblyopia. *Vision Res* 1978; 18: 931–6.

58 Hess RF Contrast sensitivity assessment of functional amblyopia in humans. *Trans Ophthalmol Sock UK* 1979; 99: 391–7.

59 Hess RF, Pointer JS Differences in the neural basis of human amblyopia: the distribution of the anomaly across the visual field. *Vision Res* 1985; 25: 1577–94.

60 Enoch JM, Birch DG, Benedetto MD. Effect of uniocular occlusion on selected visual functions *Trans Ophthalmol Soc UK* 1979; 99: 407–12.

AJO
AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 00029394 October 1990 Series 3, Vol. 110, No. 4

TABLE OF CONTENTS

ORIGINAL ARTICLES

Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome David J. Forster, Pravin U. Dugel, George T. Frangieh, Peter E. Liggett, and Narsing A. Rao

Crohn's disease and retinal vascular disease Alan J Ruby and Lee M. Jampol

Complications of tissue plasminogen activator therapy after vitrectomy for diabetes Charles K. Dabbs, Thomas M. Aaberg, Hilda E. Aguilar, Paul Sternberg, Jr., Travis A. Meredith, and Alice R. Ward

Vitrectomy retinotomy aspiration biopsy of choroidal tumors David M. Fastenberg, Paul T Finger, Quintus Chess, June H. Koizumi, and Samuel Packer

Magnetic resonance imaging in the evaluation of vitreoretinal disease in eyes with intraocular silicone oil Jeffrey G. Gross, John R. Hesselink, Gary A. Press, Michael H. Goldbaum, and William R. Freeman

Histopathologic study of the Molteno glaucoma implant in three patients Benjamin Rubin, Chi-Chao Chan, Miguel Burnier, Lucille Munion, and Jeffrey Freedman

Correlations of acoustic tissue typing of malignant melanoma and histopathologic features as a predictor of death D. Jackson Coleman, Ronald H. Silverman, Mark J. Rondeau, Frederic L Lizzi, Ian W. McLean, and Frederick A Jacobiec

Magnetic resonance imaging of radiation optic neuropathy Carol F. Zimmerman, Norman J. Schatz, and Joel S Glaser

Successful medical management of *Acanthamoeba* keratitis Steven T. Berger, Bartly J. Mondino, Richard H. Hoft, Paul B. Donzis, Gary N. Holland, Michael K. Farley, and Jeremy E. Levenson

Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture Harry S. Geggel

Penetrating keratoplasty after ocular trauma Gregory S. Doren, Elisabeth J. Cohen, Steven E. Brady, Juan J. Arentsen, and Peter R. Laibson

Limbal autograft reconstruction after conjunctival squamous cell carcinoma Robert A. Copeland, Jr., and Devron H Char

Response of Bitot's spots in preschool children to vitamin A treatment Richard D. Semba, Sopandi Wirasasmita, Gantira Natadisastra, Muhilal, and Alfred Sommer

Facial nerve injury and hemifacial spasm Bartley R. Frueh, Rebecca A. Preston, and David C Musch

EDITORIALS

Multifocal intraocular lenses – better or worse? Herbert E. Kaufman

National Registry of Drug-Induced Ocular Side Effects F. T. Fraunfelder

LETTERS TO THE JOURNAL **CORRESPONDENCE** **BOOK REVIEWS**

ABSTRACTS **NEWS ITEMS**

The AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. © 1990, Ophthalmic Publishing Company. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

MICHAEL J. LUND
Subscription Correspondent

LINDA G. CLAUSEN
Records Manager

LAUREEN A. KOTT
Assistant to the Editor

LYNN ANN LINDVIG
Sales and Production

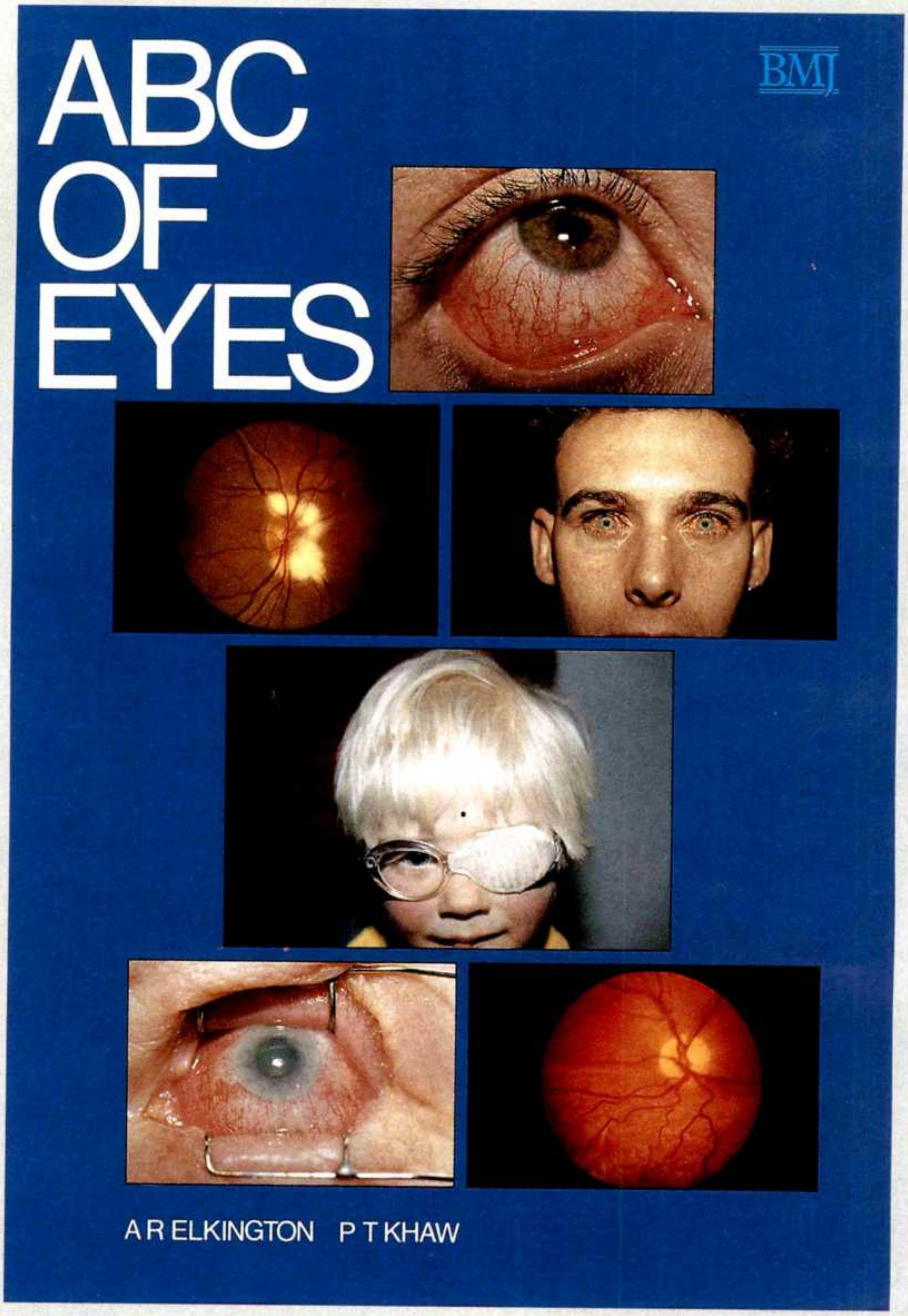
KAREN D. JOHNSON
Manuscript Editor

DIANN J. MARQUIS
Editorial Assistant

RENEE L. KASTAR
Assistant Media Planner

OPHTHALMIC PUBLISHING COMPANY

Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611, U.S.A.



Detailed descriptions of the symptoms and signs of common disorders of the eye together with **over 120 colour illustrations** make the *ABC of Eyes* an invaluable aid to diagnosis. Written by A R Elkington, senior lecturer and consultant ophthalmologist, University of Southampton, and P T Khaw, senior registrar in ophthalmology, Moorfields Eye Hospital, London, the book also provides guidance on when to refer to a specialist, and how urgently.

" . . . an excellent introduction to ophthalmology, for students and for the busy general physician . . . presents basic ophthalmology with admirable simplicity, authority and clarity."
American Journal of Ophthalmology

" . . . students and family practitioners . . . will find its short, relevant commentaries and sound clinical insights refreshing."
Canadian Medical Association Journal

Inland £10.95; Abroad £12.50
BMA members:
Inland £9.95; Abroad £11.50
including postage by air abroad

Please enclose payment with order or send us full details of your MASTERCARD, VISA or AMERICAN EXPRESS credit card.

ORDER FROM British Medical Journal, PO Box 295, London WC1H 9TE or any leading bookseller

British Journal of Ophthalmology, 1990, 74, 681–684

The electroretinogram in minimal diabetic retinopathy

T C A Jenkins, J P Cartwright

Abstract

The pattern and diffuse flash electroretinograms were measured in 20 normal subjects and 40 diabetic patients who had either normal fundi or microaneurysms only. The amplitudes of the pattern electroretinogram were found to be similar in both normals and diabetics. In the case of the flash electroretinogram the diabetic patients showed a division into two main groups. One group was not dissimilar to the group of normal subjects, while the second group showed hypernormal amplitudes. No explanation could be given, from the data collected, for this subdivision, though it is suggested it might reflect the degree of metabolic disturbance.

We have recently been connected with work that involves the monitoring of visual changes in eyes with minimal diabetic retinopathy. The battery of tests involved included fundus photography and a number of vision assessments such as colour vision, contrast sensitivity, and critical fusion frequency. It did not, however, include initially any electrodiagnostic test, and this paper arises from an assessment as to whether or not electroretinography would be a useful addition.

Several features of the electroretinogram (ERG) have been studied in diabetic retinopathy. Perhaps the oscillatory potentials (OPs) have given rise to more reports than any other. There seems to be no doubt that they are affected at some stage, but it is more likely that it is in the later preproliferative stages that they are most seriously affected[1-3] and that actual prognostic evaluation concerning proliferative development is not insignificant.[4-6] Coupland[7] suggests that there is not only a reduction of OP amplitude below normal in diabetic patients with background retinopathy but also in those with no background retinopathy. However, Arden *et al*[8] suggest that in individual patients OP amplitude is not a particularly good indicator of the disease's progress, though they agree that there is a general deterioration in the OPs with severity. Lovasik and Spafford[9] investigated 30 young insulin dependent patients with normal retinal vasculature and found significant differences, but they were so small that they were not considered diagnostic.

Amplitudes of the diffuse flash ERG, in themselves, have not been as widely studied. Certainly as a reflection of receptor activity[10] it would not be surprising if they were affected. Perlman[11] points out that the wave can be taken to represent the input to the proximal retina and the b wave its output. However, most studies concern themselves with very late stages of retinopathy and deal with retinal function before and after photocoagulation.[12-14] Gjotterberg[1] noted an interesting tendency to hypernormal amplitudes in background retinopathy, whereas those at the proliferative stage showed subnormal values. He makes the point that striving for conditions to produce maximum amplitudes is not necessarily best. The problem with an intense light flash is that, although very large waves can be produced, the dispersion of light within the eye, even in normals, occurs in an unpredictable fashion. In the present work we deliberately chose a low flash intensity to attempt to keep intersubject variability, within normals, to a minimum.

It has been suggested[10] that the pattern ERG (PERG) produced by a reversing black and white check pattern reflects ganglion cell activity, and, while it may be useful in diseases of the optic nerve and ganglion cell body, it may be less useful in diabetic retinopathy, particularly in minimal retinopathy.[7] According to Arden *et al*[8] a reduction in PERG amplitude appears at the phase of the disease when referral to an ophthalmologist is necessary. They suggest no difference occured between a group of diabetic patients with normal fundi and a group with microaneurysms only, though a difference-of-means test on their data suggests this might not have been conclusive. Because these gradings corresponded to those of the present study a PERG was undertaken as a confirmatory experiment.

Patients and methods

Two groups of subjects were invovled in the work and all gave their consent after being given an explanation of the nature of the experiments.

The diabetic group consisted of 40 non-insulin dependent patients who were passing through the clinics of the Bradford University diabetic visual screening programme. The age range was preset at 40–65 years, and all those involved had been diagnosed as diabetic for at least four years. The mean time was in fact 9·9 (range 4–28) years. All patients had to have an acuity of at least 6/9, corrected if necessary, and any eye condition other than diabetes excluded them. The possession of clear media was also a criterion for inclusion in the group.

At the beginning of the experiments full details of all patients were available, including non-stereoscopic photography. Fundus classification was based on a single photograph of the central 30° rather than on a more extensive set of photographs,[15] and patients were to have minimal retinopathy. Quite deliberately 20 were chosen with normal fundi (classed as level 10) and 20 with microaneurysms only (classed as level 20). The mean age of the total group was 54·3 (SD6·8) years, and the range reached the preset value of 40–65 years.

Clinical Vision Research Unit, Department of Optometry, University of Bradford, West Yorkshire BD7 1DP
T C A Jenkins
J P Cartwright

Correspondence to
T C A Jenkins.

Accepted for publication
7 June 1990

The normal group consisted of 20 people with no history of eye disease and who presented no abnormality on examination. A minimum level of 6/9 acuity was kept to as in the diabetic group, and as close an age match with the diabetic group was made as practicable within the stated age band. The mean age of the 20 subjects in this group was 52·6 (SD6·1) years, with the actual range 42–64 years.

A Nicolet CA 1000 clinical averager and Nicolet HGA 200A amplifier were employed together with a Nicolet NIC 1015 visual stimulator to provide the PERG stimulus. The check pattern reversal stimulus subtended a field size of 30°×24° and the individual check size was 30′. To obtain this the television screen was positioned at 85 cm from the subject and a small fixation spot was used to help the maintenance of steady fixation. The luminance of the dark squares was 11 cd/m^2 and that of the light squares was 140 cd/m^2, giving a contrast of 85%.

A Grass PS 22 photic stimulator, at the lowest intensity of unity, was used to provide the flash stimulus which at a distance of 23 cm subtended a circular field of 30°. No fixation spot was provided, and the subject was simply requested to fix the centre of the light. The low intensity flash stimulus was employed in an attempt to contain the large degree of scatter that can take place in the eye when a high intensity stimulus is used.

For both the PERG and flash ERG the band pass filters were set at 1 and 50 Hz with the sensitivity at ±100 μV. A stimulus presentation rate of 4 alternations per second and 4 flashes per second were used for both the PERG and flash ERG respectively. In both cases the analysis time was 150 ms.

All runs were under photopic conditions, and subjects had an adaptive period in the room of about 10 minutes. The ambient illumination in the plane of the eyes was approximately 150 lux.

The active electrode was DTL fibre, placed under the lower lid, which was referenced to an electrode at the centre of the forehead with a ground electrode to the side of the forehead. The maximum interelectrode impedance acceptable was 4 kohm.

The PERG was recorded first, and all subjects wore a distance correction if one was present. In the case of those over 50 years of age a +0·50 sphere was added, quite arbitrarily, to compensate for the near fixation distance. The wave produced was the averaged product of 360 sweeps, though they were recorded in six runs of 60 sweeps, each run being preceeded by a six-second fixation period. Inter-run rest periods of about 20–30 seconds were given. For convenience the right eyes of subjects were used, though in the case of three diabetic patients the left eye was used. Throughout the experiments the eye not under investigation was occluded. Pupils were undilated in all cases.

A rest interval was given of about 2 minutes before measurement of the flash ERG. In this case all readings were taken from the unaided eye. A 100-sweep wave was recorded in two runs of 50 sweeps. Again, a 6-second adaptive period was given before recording began and a single 20–30 second rest interval was provided between the two runs.

In the case of the PERG the amplitude was measured from the positive peak which occurs at 50–55 ms to the following trough which occurs at 95–100 ms (after Holder[16]). The flash ERG was recorded as the b wave amplitude from the trough of the a wave to the peak of the b wave.

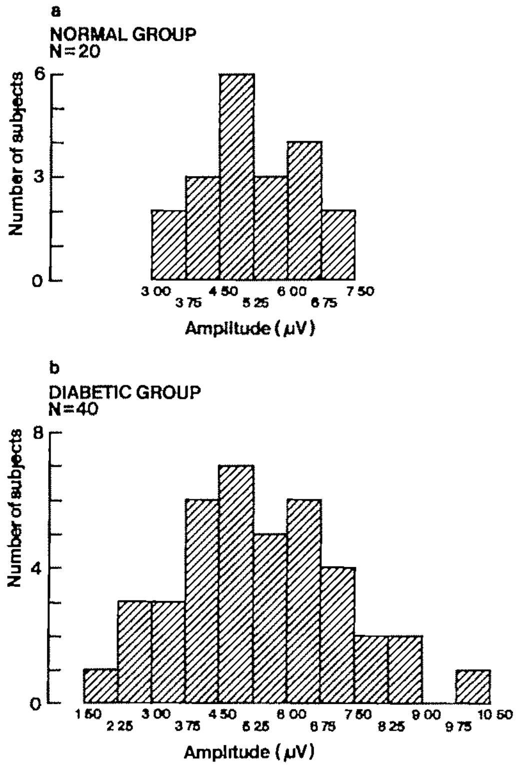


Figure 1 Histograms indicating the distribution of PERG amplitudes in (a) 20 normal subjects, (b) 40 diabetic patients.

Results

PATTERN ELECTRORETINOGRAM

Histograms indicating the PERG amplitudes for both the normal and diabetic groups are shown in Fig 1. Both sets of data appeared normally distributed when examined by a χ^2 test for normality. The mean for the normal group was 5·25 (SD1·15) μV and that for the diabetic was very close at 5·40 (SD1·85) μV. It will be seen in Fig 1 that the spread of results for the diabetic group appears greater than for the normal subjects. An F test on the variances suggested (F=2·59, p=0·01) that this was very likely to have been the case.

The individual diabetic group means were 5·68 (SD1·57) μV for level 10 and 5·13 (SD2·06) μV for level 20, though a *t* test for unrelated data showed no significant difference between them. Hence there was no evidence that the mean values for the diabetic patients were different from that of a normal age matched group.

Mean latencies for the normals were 55·02 (SD3·59) msec and 99·28 (SD9·97) for the positive peak and proceeding negative trough respectively. For the diabetic group the values differed little, and certainly not statistically significantly so, at 54·50 (SD3·84) ms and 99·65 (SD8·55) ms.

It has been reported[17] for the PERG that there is a small negative correlation between amplitude and age and a small positive one between the major positive peak latency and age. The former was confirmed here by a value of $r=-0{\cdot}26$ ($p=0{\cdot}05$) for the total subject group of 60 people, though a not significant value, of $r=0{\cdot}18$, was found for the latter. The age spread in the present investigation was, however, relatively narrow.

DIFFUSE FLASH ELECTRORETINOGRAM

Fig 2 shows histograms for both the normal and diabetic groups. While χ^2 tests for normality suggest the data of the normal subjects were normally distributed, that of the diabetic patients were not so distributed ($p=0{\cdot}01$). The mean amplitude (trough of a wave to peak of b wave) for the normal group was 36·8 (SD9·1) μV. The diabetic distribution appears bimodal in character with the two main subgroups of A and B as indicated in the figure. The mean of the 40 diabetics was 40·5 (SD11·3) μV, though clearly the use of a mean and standard deviation to describe such a distribution is very misleading. In Fig 2 such a value is very much in the trough of the distribution.

When the two main groups, A and B, were looked at in terms of a division between level 10 and level 20 patients, no relationship was found. It was certainly not true that those in group A were mainly level 10 patients and those in group B level 20. Indeed the bimodal division occurred in both level 10 and level 20 patients to about the same extent.

The subdivision appeared unrelated to the patient's age or to the length of time diagnosed as diabetic. The correlation coefficient between wave amplitude and length of time diabetic was, in fact, zero and that between amplitude and age was only 0·05.

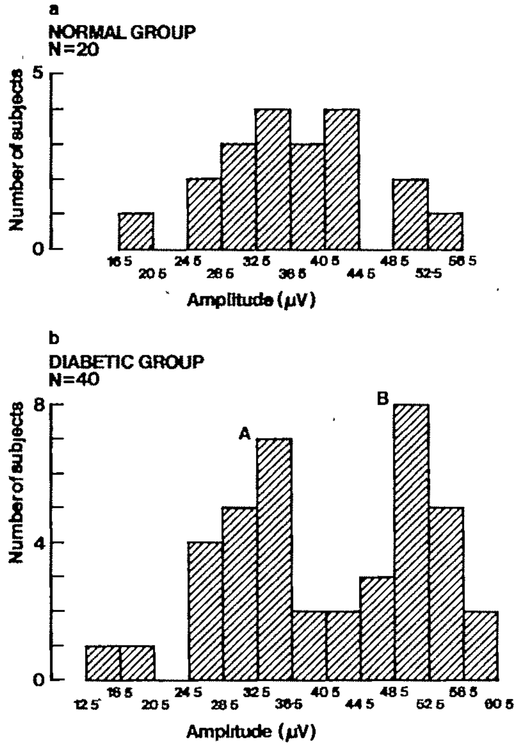


Figure 2 Histograms indicating the distribution of diffuse flash ERG b wave amblitudes in (a) *20 normal subjects* (b) *40 diabetic patients. In the case of the diabetic patients the letters A and B indicate two subgroups.*

Unfortunately, because of the impossibility of relating the subgroups to any known factor, it was impossible to decide on the exact dimensions of these subgroups. They appear perhaps appoximately equal in size, and group A values look to be not very different from those of the normal subjects. At the other extreme, 45% of the total diabetic group had amplitudes over 44 μV.

The lack of correlation between amplitude and age held for the normal group ($r=0{\cdot}13$, not significant) as well as for the diabetic group, which suggests the small inverse relationship which appears to be present for the PERG does not hold for the flash ERG. There was, however, a small ($r=0{\cdot}33$, $p=0{\cdot}01$) but statistically significant correlation between the PERG and flash amplitudes for the total group of 60 subjects. It remained at about this value for the normal group and level 10 and level 20 groups individually.

There was no evidence to suggest that the distribution of the a or b wave latencies in the diabetic group was other than a normal distribution, and there was little difference between the mean values for the normal and diabetic groups. For the former they were 20·67 (SD0·90) ms for the a wave and 39·87 (SD1·70) ms for the b wave and for the latter 20·80 (SD1·27) ms and 40·31 (SD2·65) ms respectively. Variance ratio tests suggested ($p=0{\cdot}05$ for the a wave, $p=0{\cdot}01$ for the b wave) that there was more variability in the latencies in the diabetics than in the normals.

Discussion

The results of the PERG confirmed those of previous work[8] in that there was no evidence to suggest the amplitudes of diabetics with minimal retinopathy tend to be any different from normal subjects. The values were only a little below those of Hull and Drasdo,[17] who obtained a mean amplitude of 5·68 (SD1·94) μV on normals, though because their sample contained a number of young subjects this slight increase is not surprising.

In the case of the flash ERG there was no 'a priori' reason to suspect the identification of two main groups, and indeed it was not possible to relate such groups to factors such as age, length of time diabetic, or to retinopathy level. Some estimate may be made as to amplitude values that can be considered hypernormal from the data of the normal subjects. The normal mean was 36·8 (SD 9·1) μV. For a normal distribution with such parameters 20% of subjects would be expected to have amplitudes of, or greater than, 36·8+0·84 (9·1) μV that is, 44·5 μV. When the actual data were looked at, it was seen that three people (15%) were so categorised and that this increased to 18 (45%) of the diabetic patients. If a more rigorous, 5% cut off criterion is used, then the critical value becomes, 36·8+1·65 (9·1) μV that is, 52 μV. When applied to the experimental data, this excluded one normal (5%) and seven (18%) of the diabetics.

Gjotterberg[1] found a tendency to hypernormal amplitudes in a group of diabetics with background retinopathy and argued that, since there is evidence[18] that such cases have an increased retinal blood flow, this would result in a higher ERG amplitude. It is tempting to try to interpret the present findings in such terms, though it is almost certainly too simplistic to see an increased amplitude necessarily equating to an increased blood supply.

The reason for hypernormality of amplitude in some diabetics might not even be a retinal one. Although the diabetics used in this study were defined as having clear media, it is uncertain how significant such changes would have to be to produce a dispersive effect sufficiently great to alter wave amplitude. We have carried out a study of the effect of using lightly frosted plano lenses before the eye when measuring the ERG.[19] The mildest degree of frosting used was such as to produce a lens which looked slightly dirty, thought it reduced visual acuity on a group of 10 normal subjects by only two letters on the 6/4 line. When a very low flash stimulus (unity on the Grass scale with a 7½° field size) was used, the b wave amplitude increased by nearly 60% (3·4 µV to 5·4 µV) when compared to that of a clear plano lens. Clearly low dispersive effects can make a considerable difference to ERG results.

Recent work by U Dhanesha *et al* (personal communication, 1990), using a similar group of diabetics, has also produced bimodality in the data. They made psychophysical determinations of visual functioning and showed that the results divided into two main groups according to the degree of metabolic disturbance in the patients. It is tentatively suggested that the ERG findings described here might be a further indication of such a division.

1 Gjotterberg M. The electroretinogram in diabetic retinopathy. *Arch Ophthalmol (kbh)* 1974; 52: 521–33.

2 Bresnick GH, Korth K, Groo A, Palta M. Electroretinographic oscillatory potentials predict progression of diabetic retinopathy. *Arch Ophthalmol* 1984; 102: 1307–11.

3 Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvick L. Oscillatory potentials, macular recovery time and diabetic retinopathy through 3 years of intensified insulin treatment. *Ophthalmology* 1988; 95: 1358–66.

4 Simonsen SE. Electroretinographic study of diabetics: preliminary report *Acta Ophthalmol (kbh)* 1965; 43: 841–3.

5 Simonsen SE Prognostic value of ERG (oscillatory potential) in juvenile diabetics. *Acta Ophthalmol (kbh)* 1975; 123 (suppl): 223–4.

6 Moschos M, Panagakis E, Augelopoulos A. Changes of oscillatory potentials of the ERG in diabetic retinopathy. *Ophthalmic Physiol Opt* 1987; 7: 477–9.

7 Coupland SG. A comparison of oscillatory and pattern electroretinogram measures in diabetic retinopathy. *Doc Ophthalmol* 1987; 66: 207–18.

8 Arden GB, Hamilton AMP, Wilson-Holt J, Ryan S, Yudkin JS, Kurtz A. Pattern electroretinograms become abnormal when background diabetic retinopathy deteriorates to a preproliferative stage: possible use as a screening test. *Br J Ophthalmol* 1986; 70: 330–5.

9 Lovasik JV, Spafford MM. An electrophysiological investigation of visual function in juvenile insulin-dependent diabetes mellitus. *Am J Optom Physiol Opt* 1988; 65: 236–53.

10 Maffei L, Fiorentini A. Electroretinographic response to alternate gratings before and after section of the optic nerve. *Science* 1981; 211: 953–5.

11 Perlman I. Relationship between the amplitudes of the b wave and the a wave as a useful index for evaluating the electroretinogram *Br J Ophthalmol* 1983; 67: 443–8.

12 François J, De Rouck A, Cambie E, Castanheira-Dinis A. Electrophysiological studies before and after argon laser photocoagulation in diabetic retinopathy. *Ophthalmologica* 1978, 176: 133–44.

13 Liang JC, Fishman GA, Huamonte FV, Anderson RJ. Comparative electroretinograms in argon laser and xenon arc panretinal photocoagulation *Br J Ophthalmol* 1983; 67: 520–5

14 Perlman I, Gdal-on M, Miller B, Zonis S. Retinal function of the diabetic retina after argon laser photocoagulation assessed *Br J Ophthalmol* 1985; 69: 240–6.

15 Davis MD, Hubbard LD, Trautman J, Klein R. Studies of retinopathy Methodology for assessment and classification with fundus photographs. *Diabetes* 1985; 34 (suppl 3): 42–9.

16 Holder GE. Significance of abnormal pattern electroretinography in anterior visual pathology dysfunction. *Br J Ophthalmol* 1987; 71: 166–71.

17 Hull BM, Drasdo N. The influence of age on the pattern reversal electroretinogram. *Ophthalmic Physiol Opt* 1990; 10: 49–53

18 Kohner EM. The effect of diabetes on retino-vascular function. Acta Diabetol Lat 1971; 8 (suppl 1): 135–78.

19 Douthwaite WA, Jenkins TCA, Gilmore DP. Electrophysiological investigation of simulated media opacities. Report (unpublished). University of Bradford: 1990.

British Journal of Ophthalmology, 1990, 74, 685–687

MINI REVIEW

Supply of corneal tissue in the United Kingdom

Within the last seven years in the UK there have been significant changes in the supply of corneal tissue for transplantation. Most ophthalmic surgeons here previously relied on local donors as their only source of tissue for corneal grafts. This meant that the grafts often had to be performed as emergency operations, and that excess tissue was wasted because of limited storage times and the lack of a simple routine mechanism for transferring the tissue to other hospitals. The likelihood of tissue matching for patients at high risk of immunological rejection was also severely limited. Some hospitals, notably Moorfields Eye Hospital in London and the Queen Victoria Hospital in East Grinstead, were able to schedule grafts by ensuring an adequate supply of tissue through well organised donor retrieval programmes and through the establishment of eye banks, but they were very much in the minority. The eye banks at East Grinstead and Moorfields were set up in 1959 and 1965, respectively.

Corneal Transplant Service

In 1983 the Corneal Transplant Service was inaugurated by the UK Transplant Service (UKTS) and the Iris Fund for the Prevention of Blindness with the aims of improving the availability of corneal tissue for transplantation and of reducing tissue wastage.[1] The functions of UKTS are to match and distribute organs and tissues for transplantation, to hold lists of patients awaiting transplants throughout the UK, to provide laboratory services for tissue typing including the supply of tissue typing reagents to all tissue typing laboratories in the UK, and to collect and analyse statistical data on transplantation in the UK. The Corneal Transplant Subcommittee of the UKTS Management Committee was established by the Department of Health to advise on the functioning of this new service to ophthalmologists.

The Corneal Transplant Service enables corneas that cannot be used locally to be offered through the UKTS for use in patients at other hospitals, ensuring a wide and fair distribution of tissue and greatly reducing wastage. The UKTS makes all of the necessary arrangements, including transportation, and relieves surgeons of the administrative burden involved in sharing tissue. In addition patients who are likely to suffer graft failure through immunological rejection have a far greater chance of receiving a well matched cornea, because links with other transplant teams through UKTS and Transplant Co-ordinators have increased the numbers of corneas retrieved from tissue typed multiorgan donors. Corneas from tissue typed donors are offered for patients on the national waiting list with the best tissue match.

Corneal Tissue Act 1986

Under the Human Tissues Act 1961 organs and tissues for transplantation could be removed from a donor only by a fully registered medical practitioner. There was always a chance, therefore, that eyes would not be retrieved from a donor by an ophthalmologist because of other more pressing clinical demands. In 1986 this law was amended to allow suitably trained persons who were not medically qualified to remove eyes for therapeutic, research, and teaching purposes. A course, organised by the Department of Ophthalmology in Bristol, is run specifically as a result of this Act to provide training in enucleation and storage techniques. The Corneal Tissue Act 1986 has thus reduced the likelihood of eyes not being retrieved and has brought the UK into line with other European countries and the USA. Indeed, hospitals, such as in Norwich, that have specifically employed someone to retrieve eyes have been able markedly to increase the amount of tissue collected.

Corneal Transplant Service Eye Bank

The next major advance in the supply of corneal tissue in the UK also came in 1986 when the Corneal Transplant Service Eye Bank was set up in Bristol.[2] This was a joint initiative by Bristol University Department of Ophthalmology, the UKTS, and the Iris Fund. This eye bank, which is situated in the theatre suite of the Bristol Eye Hospital, was the first in the UK to apply organ culture techniques for the storage of human corneas for transplantation.[3] Instead of storing whole eyes in moist chambers at 4°C or corneoscleral discs in tissue culture medium at 4°C, corneas are excised with a 2–4 mm scleral rim and suspended in tissue culture medium at 34°C, which extends the permissible storage time from a few hours or days to 30 days.[4-6]

When coupled with the national distribution service provided by the UKTS this capacity for extended corneal storage has a number of advantages. Perhaps the most important is that the timing of a routine graft need no longer be determined by the immediate availability of a suitable local donor, allowing grafts to be performed electively. Surgeons are now able to plan grafts well in advance simply by requesting corneas through the UKTS for the dates when they wish to graft their patients. Over 50% of grafts are scheduled with seven or more days' notice and 25% are planned more than two weeks in advance. Only 10% of grafts are performed within two days of requests being placed with the UKTS, and these are mainly emergencies. The average time between a request and the graft is 11 days, which is ample time both for the surgeons and the patients to make all necessary arrangements. Moreover only 13% of organ cultured corneas are grafted in evenings after 6 pm. Another major advantage is that corneas are always available for emergencies. The longer storage time also means that essential tasks such as donor screening for HIV and hepatitis B do not need to be done with such urgency but can be carried out at the convenience of the testing laboratory.

During organ culture, corneas are screened for bacterial and fungal contamination. At least 40% of the eyes sent to the eye bank are contaminated by bacteria (mainly *Staphylococcus* spp). Cleaning of the external ocular surface with polyvinylpyrrolidone iodine before corneoscleral disc excision and the antibiotics in the culture medium reduce the incidence of contamination during organ culture to only 7%. Contamination is revealed either through clouding of the culture medium or by routine screening of the medium during culture. All contaminated organ cultures are discarded. Thus surgeons receive tissue that should be free of bacterial and fungal contaminants, which is not the case with corneas or whole eyes stored at 4°C.

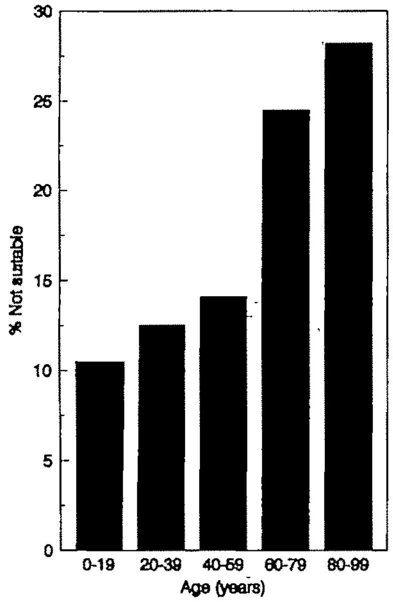


Figure 1 The influence of donor age on the proportion of organ cultured corneas discarded because of endothelial defects between 1 January 1989 and 30 June 1990. The total numbers of organ cultured corneas in each age range were: 0–19 yr, 380; 20–39 yr, 530; 40–59 yr, 810; 60–79 yr, 1365; 80–99 yr, 341.

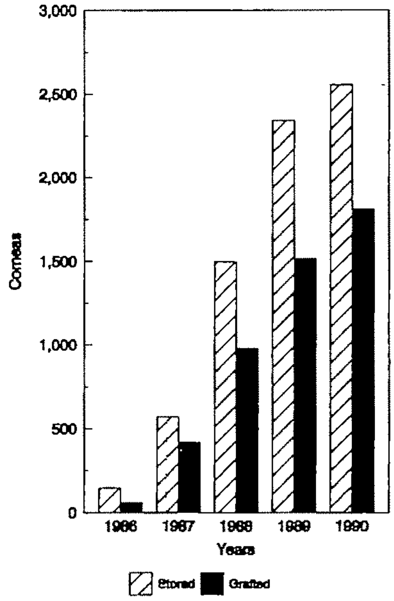


Figure 3 Corneas stored in the CTS Eye Bank in Bristol and supplied for transplantation between 1 January 1989 and 30 June 1990. The data for 1990 are extrapolated from the figures for the first six months of that year.

The corneal endothelium is carefully examined prior to transplantation to ensure an intact endothelial mosaic with an adequate density of viable cells. This allows corneas from older donors to be used with confidence and damaged corneas from younger donors that might otherwise have been used can be identified and discarded. As might be expected, the discard rate owing to endothelial defects increases with donor age, rising from approximately 10% in donors under 20 years to almost 30% in donors over 80 years (Fig 1). Overall, approximately 30% of corneas stored in organ culture are eventually discarded for a variety of reasons including inadequate endothelium, cause of donor's death, microbial contamination, and lack of HIV or hepatitis B tests (Fig 2).

In 1986 a total of 59 organ cultured corneas were supplied through the Bristol eye bank to 11 hospitals. Since then there has been a substantial rise both in the numbers of corneas stored and distributed and in the number of participating hospitals. Within three years over 1500 corneas a year were being supplied through the Bristol eye bank to over 100 hospitals throughout the UK and Eire (Fig 3). The average donor age between 1 January 1989 and 30 June 1990 was 53 years (SD 22·9, n=1802) and that of tissue typed donors was 37 years (SD 16·6, n=469) (Fig 4). During this period 26% of eye donors were tissue typed, and 80% of those tissue typed corneas were grafted into tissue matched recipients. Overall, the Bristol eye bank has supplied almost 4000 corneas for transplants in its first four years of operation.

One of the main factors in the success of this service has been the co-operation between the UKTS and the eye banks at Moorfields and East Grinstead, which use 4°C storage techniques, since excess tissue collected in the areas served by those banks can be channelled through Bristol for redistribution to other hospitals in the UK. This can be done without undue haste owing to the greater amount of time that the tissue can be stored in a viable state in organ culture. There has also been a tremendous willingness of surgeons in other hospitals to retrieve eyes not required for their own immediate needs.

Corneal transplant service eye bank network

In 1988 the David Lucas Eye Bank was opened in Manchester. This facility also stores corneas by organ culture and is fully integrated within the Corneal Transplant Service. The pattern in the UK has thus shifted from corneas being procured and used locally to the majority of corneal tissue being supplied through a loose network of four eye banks situated at Bristol, East Grinstead, Manchester, and Moorfields. In 1989 alone, over 2000 corneas were supplied for grafts through these four eye banks. This system has the advantage that just a few eye banks serve a wide geographical area in an efficient and cost effective manner. Surgeons throughout the UK are offered the widest possible choice of corneal tissue for their patients, and special needs such as for

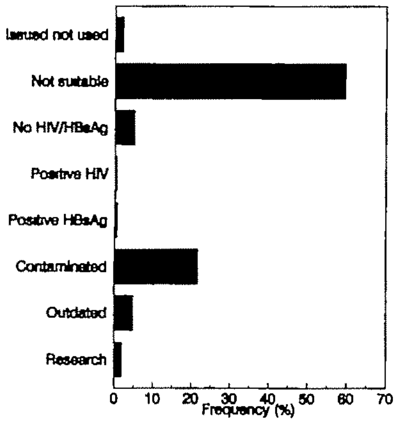


Figure 2 Discarded corneas between 1 January 1989 and 30 June 1990. A total of 1083 corneas were discarded out of 3426 stored (32%). The category 'Not suitable' includes corneas rejected because either the donor's cause of death was a contraindication for transplantation or the endothelium was unsuitable for transplantation.

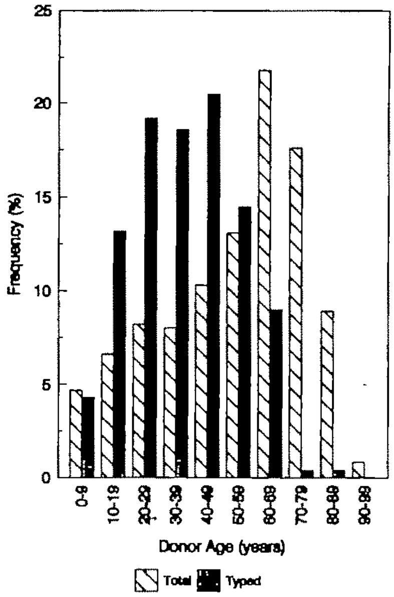


Figure 4 Age distributions of all donors (n=1802) and of tissue-typed donors (n=469) of eyes received by the CTS Eye Bank in Bristol between 1 January 1989 and 30 June 1990.

tissue matched corneas or for corneas from young or infant donors are far more likely to be satisfied. It would seem pointless to promote numerous small eye banks each serving a small population, since this would greatly increase the unit costs of storing corneas, reduce the choice of tissue for the local surgeons, and greatly complicate the logistics of sharing corneas. At present cost of storing a cornea at Bristol is approximately £70. This figure is based on the annual cost of staff, consumables, and services divided by the number of corneas supplied for grafts. Such a low figure is achieved solely because of the large number of corneas supplied – namely, about 2000 a year.

It would not be appropriate for every eye bank to use organ culture as the storage method of choice. Indeed this could be detrimental in that it would reduce flexibility of the eye bank network in the UK. It is quite clear that many eye banks require only short-term 4°C storage to function, as demonstrated by the Moorfields eye bank and the highly successful eye banks in the USA. To achieve the wide national distribution of corneas in an efficient and calm manner, however, the extended storage period offered by organ culture is of immense value.

The organ culture technique was developed in Minneapolis in the early 1970s[4,5] but is little used in the USA. Organ culture has, however, been used for a number of years in the eye banks in Arhus, Amsterdam, Vienna, and Hamburg, allowing these few eye banks to serve the needs of wide geographical areas. This applies especially to the eye banks at Arhus and at Amsterdam, the latter being closely associated with Eurotransplant, which provides similar organ matching and distribution services to the UKTS for the Benelux countries, West Germany, and Austria. To promote eye banking within Europe, the European Association of Eye Banks was inaugurated in 1989 at a meeting arranged by Professor Neils Ehlers in Arhus. The exchange of tissue typed corneas within Europe via national distribution services such as the UKTS and Eurotransplant has already been instituted.

Corneal transplant follow-up study

The data collection potential of the UKTS has been utilised for the analysis of corneal transplant follow-up data. The Corneal Transplant Study was set up to collect data on a UK national basis to investigate the influences of tissue matching, as well as clinical, surgical, and constitutional factors on graft survival.[7] The data will be analysed by multifactorial methods developed for the analysis of renal transplant data[8] that take into account interrelationships between the various factors. The statistical methods allow the simultaneous estimation of effects on graft survival, distinguish between acute and chronic influences, and make provision for unrecorded aspects of centre individuality. This study will provide an assessment of the efficacy of organ culture for corneal storage compared with 4°C storage methods.

Future prospects

The McCarey-Kaufman medium for the storage of corneoscleral discs at 4°C was devised in 1974.[9] Recently there has been renewed interest in this area, and a number of new solutions have been proposed,[10,11] though none has yet been able to provide the 30 days of storage permissible with organ culture. The advantages of storage at 4°C are purportedly simplicity and low cost, though when applied on a large scale with adequate facilities and expertise organ culture is also straightforward and inexpensive.

Cryopreservation at −196°C has the potential for providing virtually indefinite storage,[12] though a reliable technique for the cryopreservation of corneas has yet to be developed.[3,13] Should such a technique become available, eye banks would have at their disposal a complete range of short, medium, and long term techniques for storing viable corneas. Cryopreservation would perhaps be most useful for storing excess corneas and corneas from tissue typed donors that have no matched recipients. Moreover, cryopreservation offers the prospect of a bank of tissue for use in major disasters anywhere in the world.

We thank the following for their generous and continuing support of the Corneal Transplant Service. Mrs Susanna Burr, Iris Fund for the Prevention of Blindness, Col S Gaussen and Mrs Christine Wilkins, National Eye Research Centre; Mr Paul Bowerman, Bristol CTS Eye Bank, Mr T Casey, Queen Victoria Hospital, East Grinstead; Mr A Steele and Mrs S Ritten, Moorfields Eye Hospital, Mr A Ridgway and Mr Borys Marcyniuk, Manchester Royal Eye Hospital; members of the Corneal Transplant subcommittee of the UK Transplant Service Management Committee; and Rotary Club Districts 110 and 120

W J ARMITAGE
S J MOSS
D L EASTY

Department of Ophthalmology,
University of Bristol,
Lower Maudlin Street,
Bristol BS1 2LX

B A BRADLEY

UK Transplant Service,
Southmead Road, Bristol BS10 5ND

1 Bradley BA. Corneal supply in the United Kingdom. *Trans Ophthalmol Soc UK* 1986; 105: 397–400.
2 Easty DL, Carter CA, Lewkowicz-Moss SJ Corneal cell culture and organ storage. *Trans Ophthalmol Soc UK* 1986; 105: 385–96.
3 Armitage WJ, Moss SJ. Storage of corneas for transplantation In Easty DL, ed *Current ophthalmic surgery* London: Baillière Tindall, 1990
4 Summerlin WT, Miller GE, Harris JE, Good RA The organ-cultured cornea an in vitro study. *Invest Ophthalmol Vis Sci* 1973; 12: 176–80.
5 Doughman DJ, Harris JE, Schmitt MK Penetrating keratoplasty using 37°C organ cultured cornea. *Ophthalmology* 1976, 81: 778–93.
6 Pels E, Schuchard Y. Organ-culture preservation of human corneas *Doc Ophthalmol* 1983; 56: 147–53.
7 Easty DL, Rogers CA, Gore SM, Bradley BA, Karwatowski WS. Corneal Transplant Follow-up Study (CTFS). *Invest Ophthalmol Vis Sci* 1990; 31: 270.
8 Gilks WR, Bradley BA, Gore SM, Selwood NH. Immunogenetic and clinical factors affecting renal transplantation – a rigorous analysis of data recorded by the UK Transplant Service. *Transplantation* 1986; 42: 39–45.
9 McCarey BE, Kaufmann HE Improved corneal storage. *Invest Ophthalmol Vis Sci* 1974; 13: 165–73
10 Lindstrom RL, Skelnik DL, Lass J, *et al*. Optisol – a new 4°C corneal preservation solution. *Invest Ophthalmol Vis Sci* 1990; 31: 475.
11 Laing RA, Hirokawa K, Yang ZR, Oak S Maintenance of corneal endothelium in storage media. *Invest Ophthalmol Vis Sci* 1990; 31: 268.
12 Armitage WJ. Cryopreservation of animal cells In Bowler K, Fuller BJ, eds *Temperature and animal cells*. Society for Experimental Biology Symposium No. 41. Cambridge: Company of Biologists, 1987. 379–93.
13 Taylor MJ. Clinical cryobiology of tissues preservation of corneas. *Cryobiology* 1986; 23: 323–53.

British Journal of Ophthalmology, 1990, 74, 688–693

CASE REPORTS

Multifocal posterior uveitis: clinical and pathological findings

David G Charteris, William R Lee

Abstract

A pathological study was performed on the necropsy eyes of a 59-year old-woman who had suffered for nine years from multifocal posterior uveitis. The disease had been controlled by steroid therapy with good preservation of visual function. Extensive investigation did not reveal the aetiology. On macroscopic examination numerous focal lesions with various degrees of pigmentation were observed scattered across the fundi. These lesions were studied by light and electron microscopy and immunohistochemistry. There was ongoing chorioretinal inflammation in the foci, producing destruction of Bruch's membrane, the retinal pigment epithelium (RPE), and the outer retina. The focal scars showed migration of RPE and glial cells and neovascularisation. Capillary and venule endothelial cells were swollen at the inflammatory sites. Attempts to establish a cause for this condition were unsuccessful.

Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh, and Departments of Pathology and Ophthalmology, Tennent Institute, Western Infirmary, Glasgow
D G Charteris
W R Lee

Correspondence to:
Mr D G Charteris,
Department of Pathology,
Institute of Ophthalmology,
17–25 Cayton Street, London
EC1V 9AT.

Accepted for publication
31 May 1990

The pathogenesis of many forms of multifocal chorioretinal inflammatory disease remains unknown, and a lack of histopathological material has in many cases prevented an understanding of the aetiology of these conditions. In this report we describe the unexpectedly active and destructive inflammatory changes found in a case of multifocal choroiditis which clinically was thought to be quiescent.

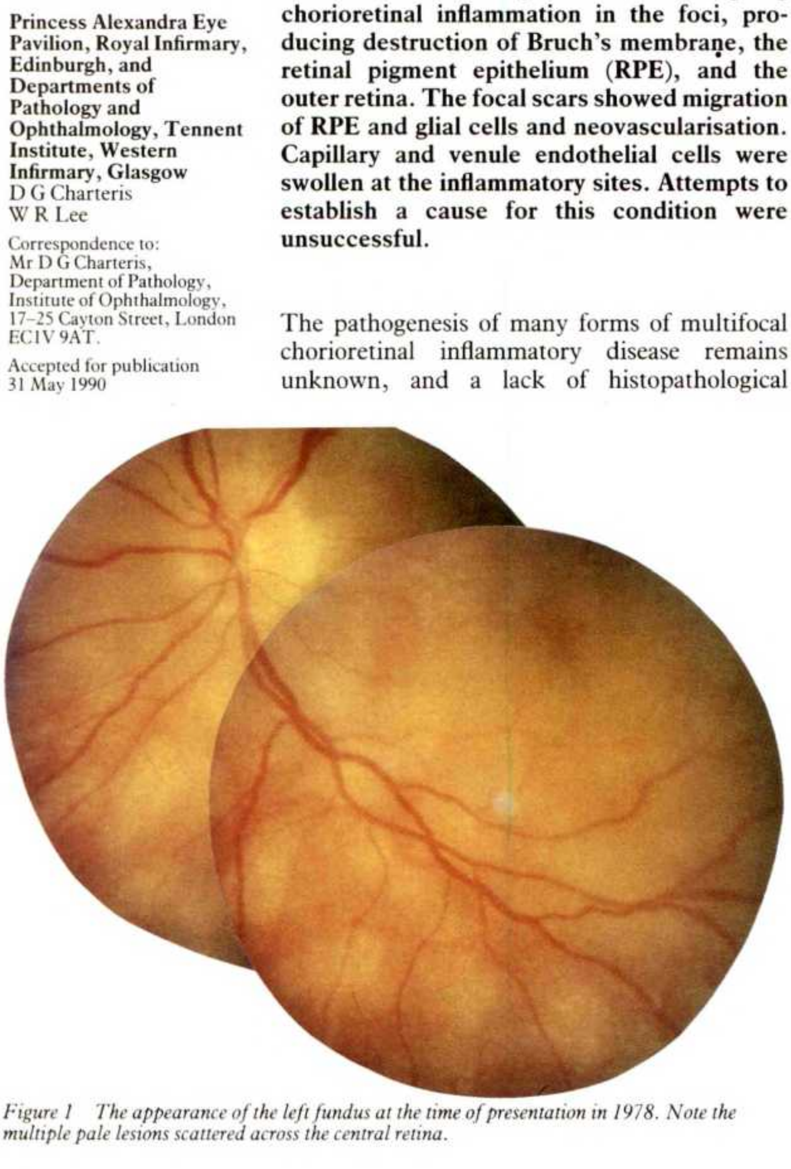


Figure 1 The appearance of the left fundus at the time of presentation in 1978. Note the multiple pale lesions scattered across the central retina.

Case report

In 1978 a 50-year-old woman presented to the eye casualty department with a one-month history of aching pain and blurring vision in both eyes. Her vision was 6/12 in the right and 6/18 in the left eye. She had mild iritis and mild optic disc oedema in both eyes. Two weeks later her vision deteriorated to counting fingers right and hand movements left. In addition to moderate anterior chamber inflammatory activity she had bilateral total exudative retinal detachments. She had no systemic illness, was on no medication, and extensive investigation including viral serology gave negative results.

Treatment with systemic prednisolone 80 mg/day resulted in rapid regression of the exudative detachments; cream coloured round patches then became evident throughout the whole extent of both fundi (Fig 1). Fluorescein angiography showed patchy late hyperfluorescence. The electro-oculogram (EOG) was reduced to 140% in the right eye and 120% in the left. A provisional diagnosis of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was made. The patient's vision gradually improved, and the steroid dose was reduced, though two transient episodes of increased activity required temporary increases in steroid dosage. One year after presentation her visual acuity was 6/9 right and 6/6 left, and there was patchy depigmentary chorioretinal scarring, with mottled pigmentation of the maculae (Fig 2).

Low dose systemic steroids were continued for a total of five years. There was mild residual anterior uveitis following systemic steroid withdrawal. The patient died in 1987 from an acute myocardial infarct. Six weeks prior to death her vision was 6/9 right and left, there was a mild bilateral anterior uveitis, and there were patches of chorioretinal scarring which did not show any clinical evidence of active inflammation.

Material and methods

The eyes were removed approximately 12 hours after death. The left eye was fixed in formal

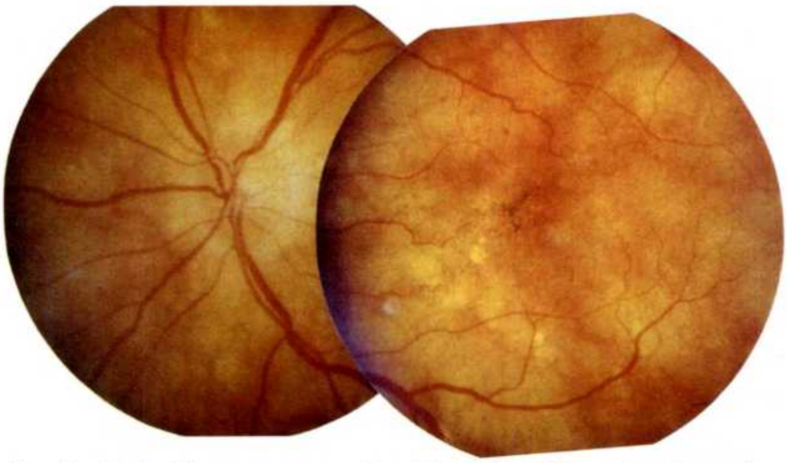


Figure 2 Left fundal appearance one year later. Note the hyperpigmentation at the macula and the loss of pigmentation elsewhere.

saline and the right in 2% cacodylate buffered glutaraldehyde. Both eyes were of normal dimensions and were divided horizontally above and below the macula.

Paraffin-histology. After paraffin embedding serial sections were taken from both paraffin blocks and stained with haematoxylin-eosin (H-E), periodic acid Schiff (PAS), and stains for axons (Bodain), myelin (Loyez), and iron (Perls). Additional blocks were taken from the calottes for immunohistochemistry and electron microscopy.

Immunohistochemistry. Sections from the formal saline fixed tissue were stained by the peroxidase-antiperoxidase (PAP) technique for B and T lymphocytes, macrophages (muraminidase, α-ACT, α-1AT), and immunoglobulins (IgA, IgG, IgM, ϰ and λ). In-situ hybridisation was employed for identification of herpes simplex viral antigen.

Electron microscopy. Macrophotographs were taken of the superior and inferior calottes from the right eye, and designated foci of hypo and hyperpigmentation were excised for study (Figs 3 and 4). Fifteen blocks were embedded in Araldite and 1 μm sections were stained with toluidene blue. Eight blocks were studied by semiserial sectioning (at 50 or 100 μm steps), and, where appropriate, ultrathin sections were taken and stained conventionally for examination in a Philips 301 electron microscope.

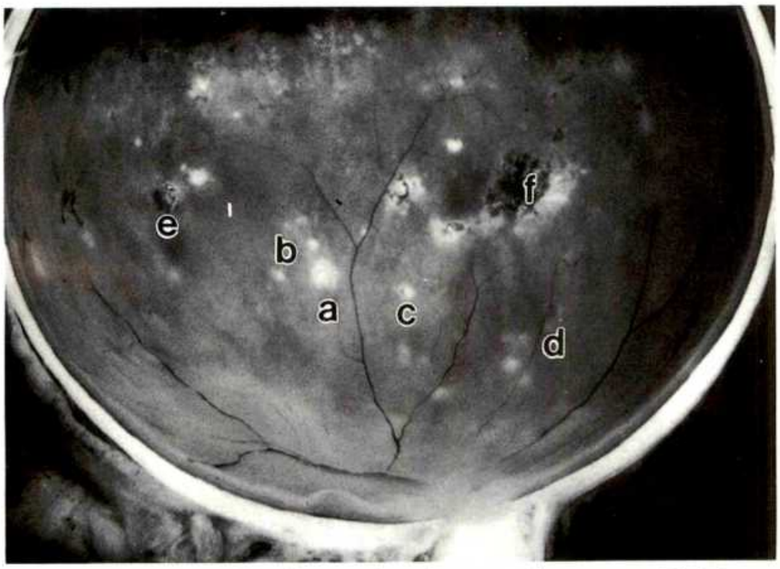


Figure 3 Inferior calotte of the right eye to show the macroscopic appearance of the lesions. EM blocks were taken from areas designated a-f (letters located below lesions).

Results

MACROSCOPIC EXAMINATION

The findings in both globes were essentially the same. The anterior segments appeared normal, and the vitreous was clear. There were meridional folds on the pars plana, but no evidence of pars planitis. Focal lesions, varying in size between 0·5 and 1·5 mm, were scattered throughout the fundus, predominantly in the mid periphery. The smallest lesions were pale and free from pigmentation, while the more obvious contained specks and clumps of pigment (Figs 3 and 4). The largest lesions were heavily pigmented with lacunae of depigmentation. The appearances of the maculae, the peripapillary retinae, and the optic discs were within normal limits for postmortem material.

MICROSCOPIC EXAMINATION

Paraffin sections

The conjunctiva, the cornea, the outflow system, and the lens were of normal architecture. The iris stroma contained scattered lymphocytes which formed aggregates at the pupil and at the root. The ciliary body contained a few clusters of lymphocytes, and there were non-specific proliferative changes in the epithelial layers of the pars plana. The vitreous was free from inflammatory cell infiltration.

At the far periphery the retinal pigment had non-specific age-related degenerative changes, and occasional drusen were observed. The inner retina was well preserved, and the nerve fibre layer and optic nerve contained axons of normal density.

At the macula there was depletion of nuclei in the outer nuclear layer; here the photoreceptors showed autolytic changes. Clusters of lymphocytes were noted in the posterior choroid and in the adventitia of some of the posterior ciliary vessels and nerves. A study of designated representative lesions (Figs 3 and 4) was made from plastic embedded matrial.

Plastic embedded histology

The following description is derived from blocks taken from the sites designated in Figs 3 and 4. Where appropriate light microscopy was supplemented by electron microscopy. The descriptions relate to the centre of the lesions.

The small non-pigmented lesions were of variable histological appearance. In three blocks (Fig 4, lesions P, T, and W) there was a lymphocytic infiltration in the choroid, with some cellular infiltration in the hypopigmented retinal pigment epithelium (Fig 5); the overlying retina showed minor atrophy of the photoreceptor layer. Electron microscopy showed the cells within the retinal pigment epithelium (RPE) to be macrophages (Fig 5C) and the outer segments to be adequately preserved (Fig 5b). By contrast in a somewhat similar macroscopic

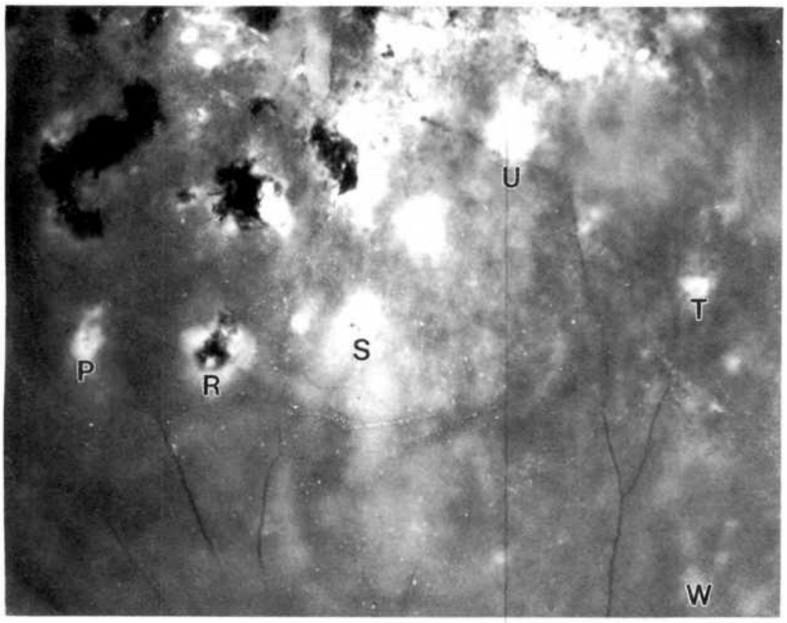


Figure 4 The appearance of the superior calotte to show in more detail the characteristic lesions. EM blocks were taken from the areas designated P-W.

lesion (Fig 3, lesion b) the RPE was replaced by glial scar tissue which had penetrated Bruch's membrane and had destroyed the choriocapillaris. Beneath this lesion there was a cluster of lymphocytes adjacent to a myelinated nerve bundle. It was noteworthy that in almost every block examined branches of ciliary nerve were observed in association with the lymphocytic clusters within the choroid.

Partially pigmented lesions also varied in their histological appearance. In three blocks (Fig 3, lesions a, c, and d) Bruch's membrane was interrupted by small breaks but was easily identifiable. In lesion c the photoreceptor layer was replaced by glial cells which abutted on to Bruch's membrane (Fig 6a). In lesions a and d (Fig 3) the RPE was multilayered and infiltrated by macrophages and lymphocytes (Figs 6b, c). Over these areas of RPE disturbance there was outer retinal atrophy of varying degrees. The choriocapillaris was either normal, infiltrated by inflammatory cells, or replaced by collagenous

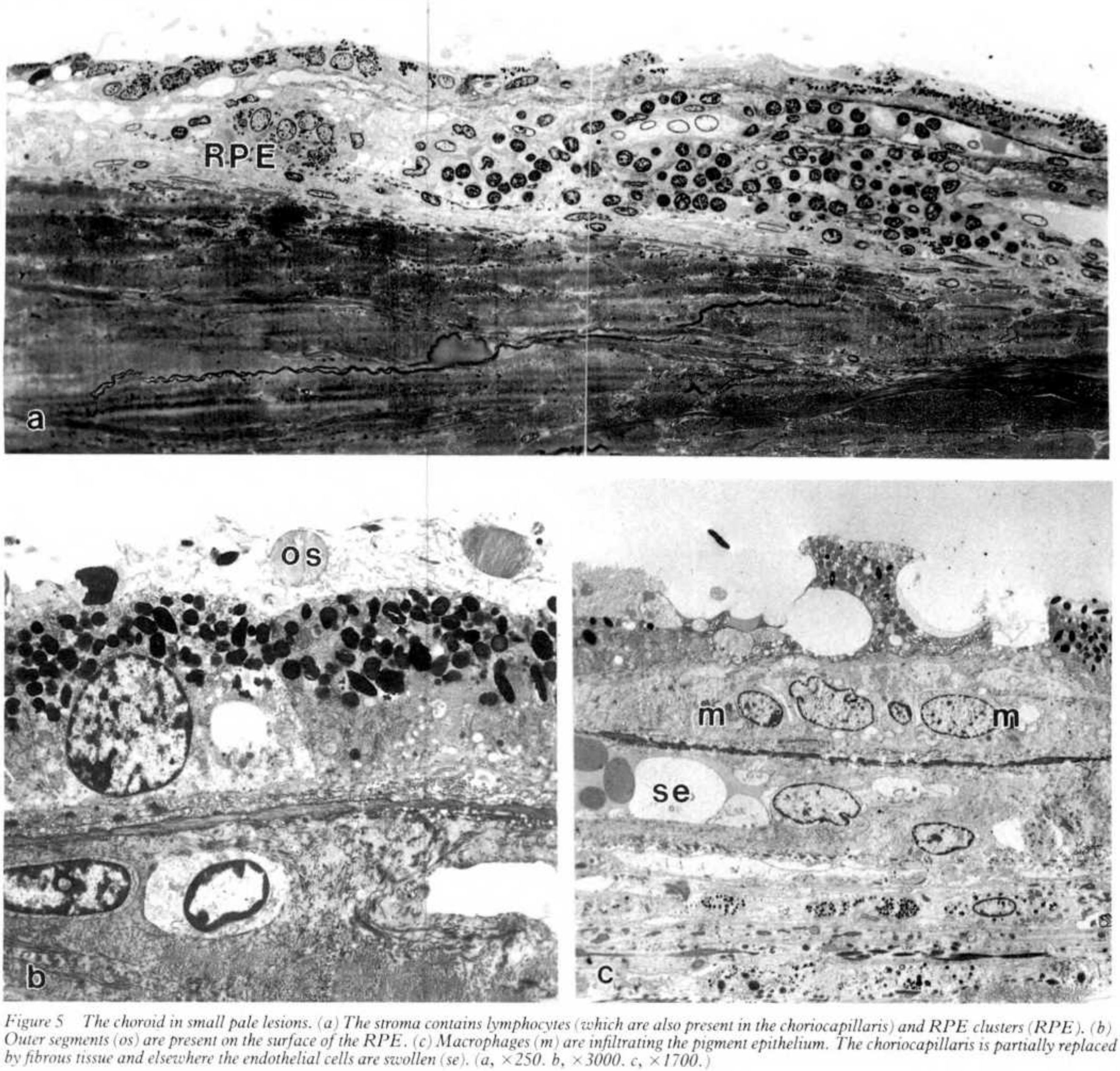


Figure 5 The choroid in small pale lesions. (a) The stroma contains lymphocytes (which are also present in the choriocapillaris) and RPE clusters (RPE). (b) Outer segments (os) are present on the surface of the RPE. (c) Macrophages (m) are infiltrating the pigment epithelium. The choriocapillaris is partially replaced by fibrous tissue and elsewhere the endothelial cells are swollen (se). (a, ×250. b, ×3000. c, ×1700.)

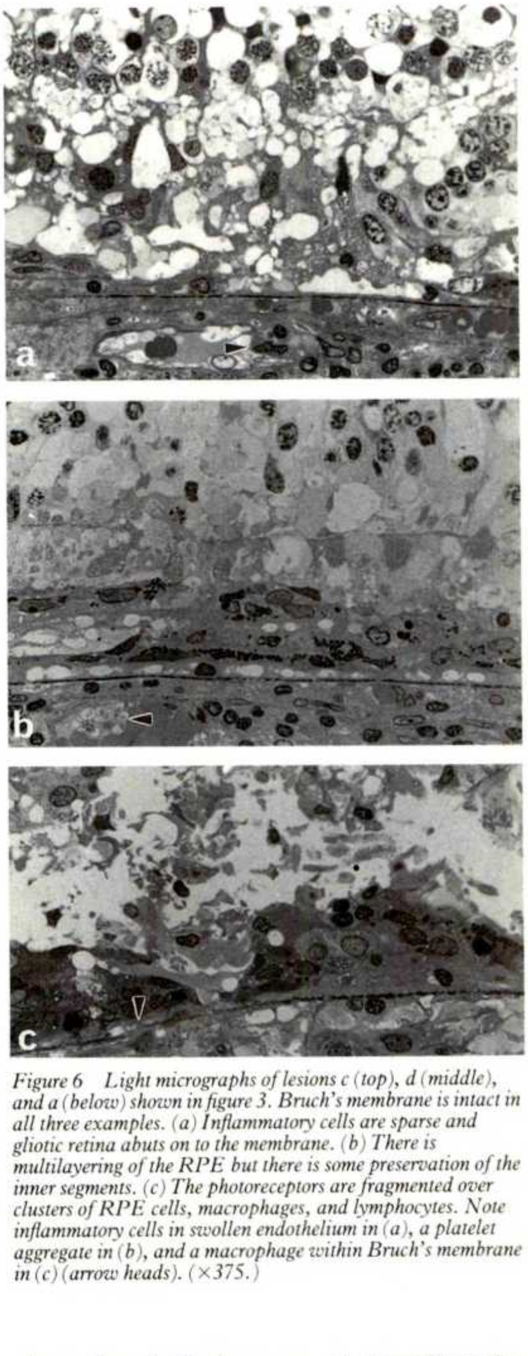


Figure 6 Light micrographs of lesions c (top), d (middle), and a (below) shown in figure 3. Bruch's membrane is intact in all three examples. (a) Inflammatory cells are sparse and gliotic retina abuts on to the membrane. (b) There is multilayering of the RPE but there is some preservation of the inner segments. (c) The photoreceptors are fragmented over clusters of RPE cells, macrophages, and lymphocytes. Note inflammatory cells in swollen endothelium in (a), a platelet aggregate in (b), and a macrophage within Bruch's membrane in (c) (arrow heads). (×375.)

tissue. Invariably there were clusters of lymphocytes in the choroidal stroma.

In other partially pigmented lesions the inflammatory process was more destructive (Fig 3, lesion e, Fig 4, lesion s). In these it was difficult to identify Bruch's membrane. The outer retina was invaded by lymphocytes, macrophages, RPE cells, and capillaries (Fig 7).

Swelling and cytoplasmic rarefaction of endothelial cells in choroidal capillaries and venules was a constant feature irrespective of the degree of inflammatory destruction (Figs 5, 6a, and 7). At the ultrastructural level the junctions between these endothelial cells were intact, but lymphocytes were often found in close relationship with the endothelial cells (Fig 6a). In some vascular lumina there were platelet clusters (Fig 6b), but neither fibrin, thrombi, nor immune complex deposits were identified. There was no evidence of previous choroidal vascular occlusive disease as shown by hyalinisation of the intima or media. Migration of RPE cells into the choroid was seen in lesions of varied appearance and degree of destruction (Figs 5 and 7).

Two heavily pigmented foci were studied (Fig 3, lesion f, and Fig 4, lesion R). These consisted of atrophic retina in all layers over a band of multilayered and hyperplastic RPE cells with an admixture of macrophages. There was a dense choroidal inflammatory infiltrate. At the periphery of even advanced lesions the photoreceptor outer segment architecture was preserved, and evidence of photoreceptor phagocytosis by exogenous macrophages was obtained (Fig 8).

In none of the sections examined at the light or ultrastructural level was it possible to identify structures with protozoal, viral, or bacterial characteristics.

Immunohistochemistry

Within the choroidal infiltrate 70–80% of the lymphocytes were identified as T cells, less than 20% were B cells. Small numbers of macrophages were noted in all parts of the inflammatory foci. There was no significant deposition of immunoglobulin. In-situ hybridisation for identification of herpes simplex virus gave negative results.

Discussion

The case was initially diagnosed as acute posterior multifocal placoid pigment epitheliopathy (APMPPE)[1] because of the multiple pale inflammatory lesions seen across the posterior fundi. Exudative retinal detachments have been described as an unusual presenting feature of APMPPE,[2] and more recent reports have stressed that APMPPE can be chronic or recurrent.[3-5] However, the presentation and subsequent course of the disease are more typical of Harada's disease.[6-8] Similarities between these two conditions have been noted, and it has been suggested that they represent a continuous spectrum of disease.[9] This case has the ocular picture of Harada's disease without the systemic manifestations and therefore best fits an intermediate group as defined by Wright, Bird, and Hamilton.[9] Because of the difficulties in categorising the case we have elected to refer to it in the broader clinical context of multifocal posterior uveitis.

The histopathological characteristics of the lesions identified in the choroid and retina include a deep choroidal lymphocytic infiltrate (usually associated with a myelinated nerve), with extension to the choriocapillaris and variable breaks in Bruch's membrane. Thickening of the RPE was due to proliferation of the native RPE cells (with and without melanin depletion) and to infiltration by macrophages and lymphocytes. The restricted focal nature of the lesions was impressive, as was the sparing of the adjacent retina. Indeed it appeared that involvement of the photoreceptor layer could be regarded as the destruction of an innocent bystander. The pattern of cellular infiltration is similar to that found by Perry and Font in cases of Harada's disease,[7] although we found few plasma cells within the infiltrate.

It has been suggested that both APMPPE and multifocal choroiditis may be initiated by choroidal ischaemia.[9-11] With reference to this

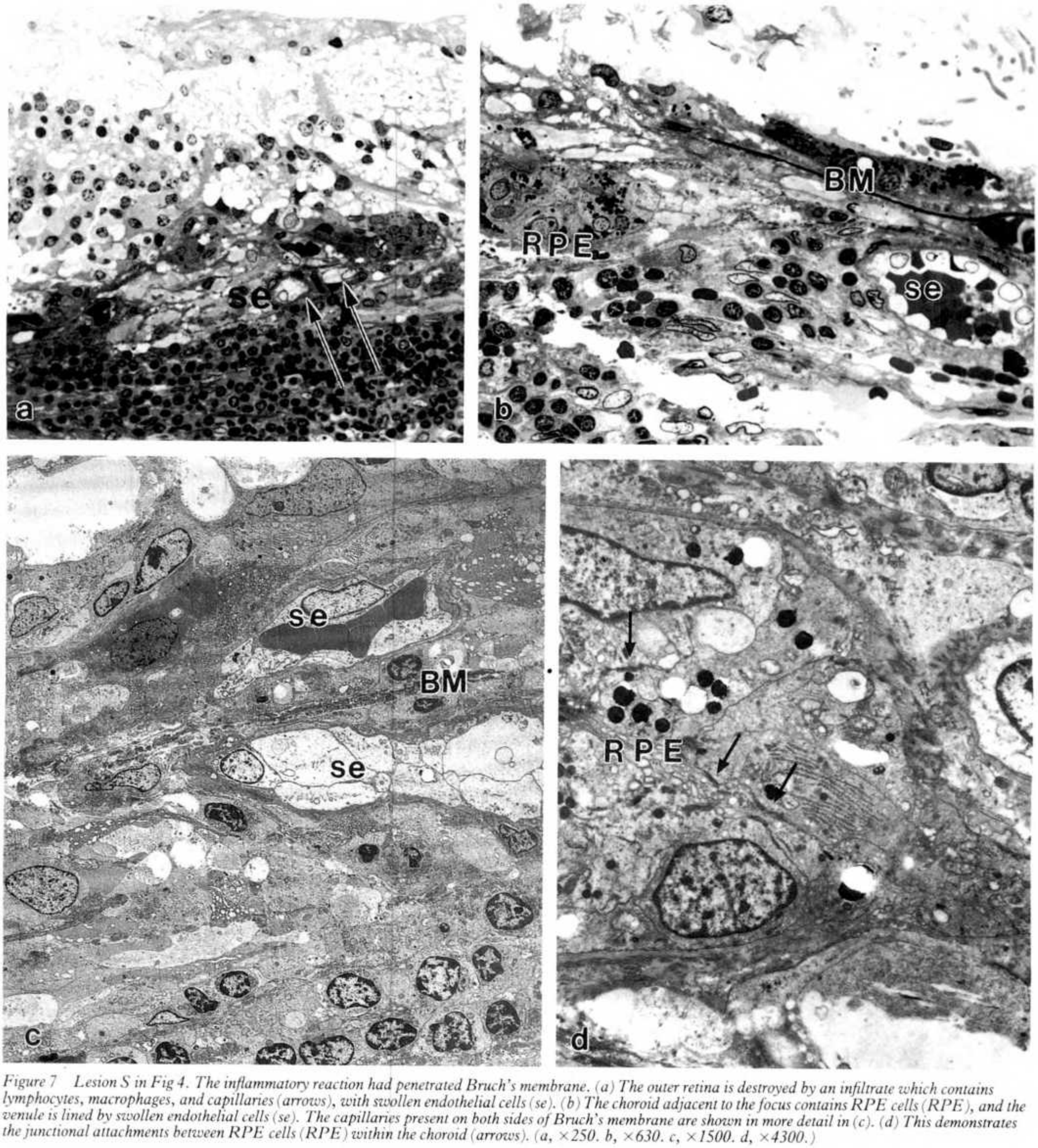


Figure 7 Lesion S in Fig 4. The inflammatory reaction had penetrated Bruch's membrane. (a) The outer retina is destroyed by an infiltrate which contains lymphocytes, macrophages, and capillaries (arrows), with swollen endothelial cells (se). (b) The choroid adjacent to the focus contains RPE cells (RPE), and the venule is lined by swollen endothelial cells (se). The capillaries present on both sides of Bruch's membrane are shown in more detail in (c). (d) This demonstrates the junctional attachments between RPE cells (RPE) within the choroid (arrows). (a, ×250. b, ×630. c, ×1500. d, ×4300.)

hypothesis we did not find immune complexes or fibrinoid necrosis in blood vessels, nor was there any evidence to suggest a previous inflammatory vasculopathy which had produced choroidal vascular hyalinisation and luminal narrowing. There was no evidence of current bacterial, fungal, viral, or protozoal infection.

The evolution of the destructive process appeared to depend on the preservation of Bruch's membrane. If the membrane survived the initial inflammatory insult, the RPE responded by proliferation and formation of layers of collagen. An intact Bruch's membrane did not necessarily protect the RPE and photoreceptor layer. RPE loss and photoreceptor destruction were seen despite the preservation of the underlying membrane, and we demonstrated that inflammatory cells may gain access to the outer retina through small breaks in an otherwise intact Bruch's membrane (Fig 6).

There was notable photoreceptor survival despite ongoing inflammation within the foci. The long term survival of photoreceptors contrasts with the early lysis of rod outer segments reported in experimental autoimmune uveitis.[14] Our evidence suggests that photoreceptor outer segments are not the primary autoimmune target in this form of human disease.

Glial cell migration from the retina to the choroid has been described in syphilis[15] and other inflammatory conditions.[16] The occurrence of this abnormality in multifocal posterior uveitis

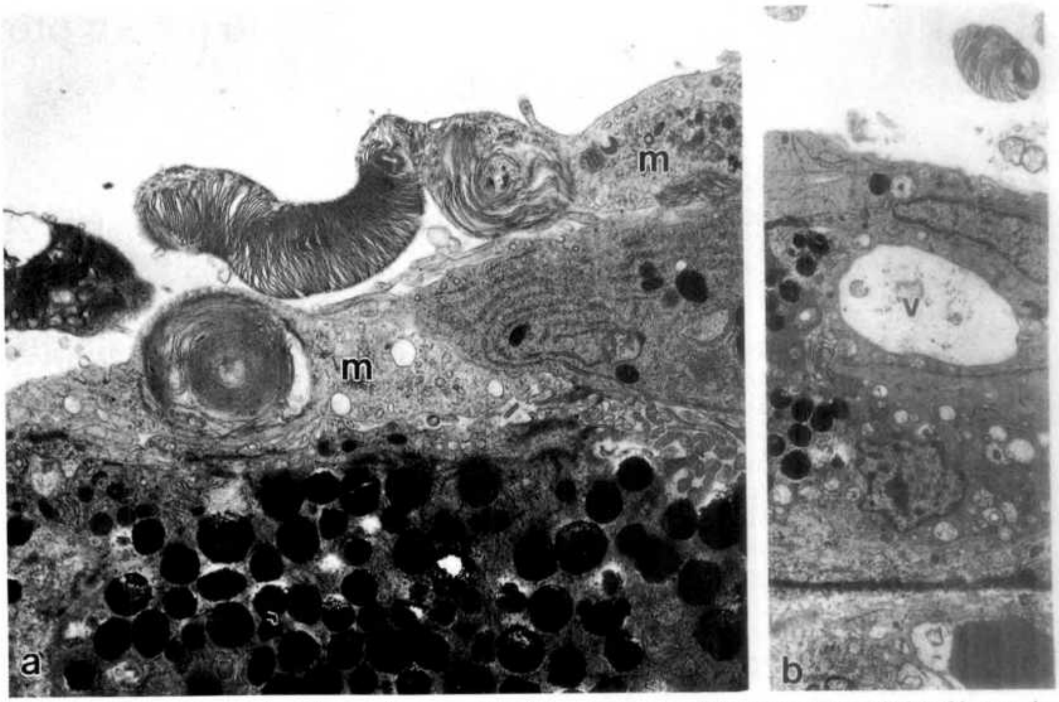


Figure 8 Electron micrographs to illustrate the preservation of the outer segments of the photoreceptors, which in this example are phagocytosed by macrophages (m). Some RPE cells contain vacuoles (v). (a, ×6000. b, ×2480.)

is further evidence of the non-specific nature of the glial cell activity. Similarly migration of RPE cells into the choroid is now regarded as non-specific,[16] as is neovascularisation in a glial scar.[17]

Recent work has highlighted the importance of high endothelial venule (HEV) like vessels in the recruitment of lymphocytes into inflamed tissues.[18, 19] The term 'high endothelial venule' is applied to the post-capillary venules of lymph nodes and to vessels in inflamed tissue which morphologically have an increase in the height of their endothelial cells. These endothelial cells have histochemical alterations relating to lymphocyte-endothelial interactions and are believed to play a role in the uptake of lymphocytes to lymphatic and inflamed tissues. We frequently found this response to dense focal accumulations of lymphocytes, and we also demonstrated the presence of lymphocytes within the vessel wall. Endothelial cell swelling was demonstrated in both the choroidal venules and the choriocapillaris. The presence of such changes is of added significance in view of the recently reported association of class II major histocompatibility complex (MHC) antigen expression on endothelial cells with lymphocyte recruitment in experimental ocular inflammation.[20]

In conclusion, we have demonstrated that active, ongoing focal inflammation can occur in a case of clinically quiescent posterior uveitis. Despite detailed study we were unable to correlate the macroscopic appearance of the lesions with specific patterns of pathological change. No ischaemic or infective cause of the disorder was found.

There was migration of glial and RPE cells within the inflammatory foci and neovascularisation of the glial scars; these changes are seen in other forms of posterior uveitis. We believe that this is the first study to demonstrate the presence of high endothelial venule-like vessels at the sites of inflammation in human ocular tissue.

1 Gass JDM. Acute posterior multifocal placoid pigment epitheliopathy. *Arch Ophthalmol* 1968; **80**: 177–85.

2 Bird AC, Hamilton AM. Placoid pigment epitheliopathy presenting with bilateral serous retinal detachment. *Br J Ophthalmol* 1972; **56**: 881–6.

3 Murray SB. Acute posterior multifocal placoid pigment epitheliopathy: Not so benign? *Trans Ophthalmol Soc UK* 1979; **99**: 497–500.

4 Damato BE, Nanjiani M, Foulds WS. Acute posterior multifocal placoid pigment epitheliopathy. A follow up study. *Trans Ophthalmol Soc UK* 1983; **103**: 517–22.

5 Gass JDM. Acute posterior multifocal placoid pigment epitheliopathy. A long term follow up. In: Fine SL, Owens L, eds. *Management of retinal vascular and macular disorders*. Baltimore: Williams and Wilkins, 1983: 176–81.

6 Ohno S, Char DH, Kimura SJ, O'Connor GR. Vogt-Koyanaga-Harada syndrome. *Am J Ophthalmol* 1977; **83**: 735–40.

7 Perry HD, Font RL. Clinical and histopathological observations in severe Vogt-Koyanagi-Harada syndrome. *Am J Ophthalmol* 1977; **83**: 242–54.

8 Chan C, Palestine A, Kuwabara L, Nussenblatt R. Immunopathological study of Vogt-Koyanagi-Harada syndrome. *Am J Ophthalmol* 1988; **105**: 607–11.

9 Wright BE, Bird AC, Hamilton AM. Placoid pigment epitheliopathy and Harada's disease. *Br J Ophthalmol* 1978; **62**: 609–21.

10 Hayreh SS. Segmental nature of the choroidal vasculature. *Br J Ophthalmol* 1975; **59**: 631–47.

11 Deutman AF, Lion F. Choriocapillaris nonperfusion in acute multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1977; **83**: 652–7.

12 Young NJA, Bird AC, Sehmi K. Pigment epithelial diseases with abnormal choroidal perfusion. *Am J Ophthalmol* 1980; **90**: 607–17.

13 Gaudric A, Coscas G, Bird AC. Choroidal ischemia. *Am J Ophthalmol* 1982; **94**: 489–98.

14 Forrester JV, Borthwick GM, McMenamin PG. Ultrastructural pathology of S-antigen uveoretinitis. *Invest Ophthalmol Vis Sci* 1985; **36**: 1281–92.

15 Blodi FC, Hervovet F. Syphilitic chorioretinitis. *Arch Ophthalmol* 1968; **79**: 294–6.

16 Green WR. Retina. In: Spencer WH, ed. *Ophthalmic pathology*. Philadelphia: Saunders, 1985: 855.

17 Green WR. Uveal tract. In: Spencer WH, ed. *Ophthalmic pathology*. Philadelphia: Saunders, 1986: 1513–4.

18 Freemont AJ, Ford WL. Functional and morphological changes in post-capillary venules in relation to lymphocytic infiltration into BCG-induced granulomata in rat skin. *J Pathol* 1985; **147**: 1–12.

19 Freemont AJ. Functional and biosynthetic changes in endothelial cells of vessels in chronically inflamed tissues: evidence for endothelial control of lymphocyte entry into diseased tissues. *J Pathol* 1988; **155**: 225–30.

20 Lightman S. Immune mechanisms in autoimmune ocular disease. *Eye* 1988; **2**: 260–6.

British Journal of Ophthalmology, 1990, 74, 694–695

Linear scleroderma associated with ptosis and motility disorders

Maria S A Suttorp-Schulten, Leo Koornneef

Orbital Centre, Department of Ophthalmology, Academic Medical Centre, Amsterdam, The Netherlands
M S A Suttorp-Schulten
L Koornneef

Correspondence to:
M S A Suttorp-Schulten, MD,
Department of Ophthalmology, Academisch Medisch Centrum,
Meibergdreef 9, 1105 Az
Amsterdam, The Netherlands.

Accepted for publication
7 June 1990

Abstract

A case is reported in which an 11-year-old girl developed progressive ptosis and a subsequent motility disorder of the right eye. The diagnosis linear scleroderma en coup de sabre was established. Atrophy of the upper levator palpebral and superior rectus muscle could be shown on CT scan.

Linear scleroderma is an uncommon dermatological disorder. It produces a unilateral bandlike linear atrophy of the skin and its underlying structures. If it involves the frontoparietal region it is called 'scleroderma en coup de sabre'.[1,2]

Sometimes symptoms are so prominent that the patient presents to an ophthalmologist long before the dermatological diagnosis has been established, as happened in our case.

Case report

The patient, a girl born in 1971, was seen elsewhere at the age of 11 years because of a slowly progressive ptosis of the right eye. The skin above the right eye showed a small linear area of induration and on the right half of the scalp there was a small area of alopecia. She underwent a right levator muscle resection. Two years later she was referred to our clinic because of recurrence of the ptosis. Her visual acuity was 20/20 in both eyes. The motility of both eyes was full. Ophthalmological examination revealed no abnormalities. There was a 6 mm ptosis of the right eye. A linear lesion of atrophic skin ran from the right forehead down to the upper eyelid with associated loss of hair of the eyebrow and cilia. On the right frontal area of the scalp there was a linear band of alopecia associated with skin atrophy and underlying bone atrophy. Again a resection of the right palpebral levator muscle was performed.

In 1987 the patient, now aged 16, again presented with another recurrence. At that time she complained of diplopia. There was a restriction of elevation and abduction of the right eye (Fig 1). A progressive myopathy was suspected but no neurological disease could be detected except for denervation of the superior levator palpebral muscle. Myasthenia gravis could be excluded. A CT scan of the orbit revealed a marked atrophy of the levator and rectus superior muscles (Fig 2). Because of the typical skin lesions, which showed progression, the patient was referred to a dermatologist, who established the diagnosis of scleroderma en coup de sabre.

Discussion

Scleroderma may occur as a systemic disease or as a localised form. The latter presents in three clinical forms: generalised, morphoea, and linear. The linear form may involve the frontoparietal region and is then called coup de sabre. It is a bandlike lesion of induration and atrophy of the skin and its underlying structures.[1] Involvement of the orbit and the eye is possible but uncommon and has not often been described, especially in ophthalmological literature. Ocular findings include corneal changes such as keratitis,[3] diminished corneal sensibility,[4] keratitic precipitates,[5-7] iris changes such as heterochromia,[8,9] sectoral atrophy,[7,10] and mydriasis

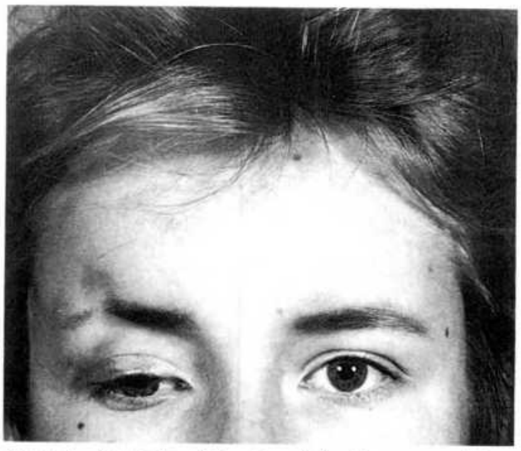


Figure 1 Restriction of elevation of the right eye, atrophic skin, and loss of hair of the right eyebrow.

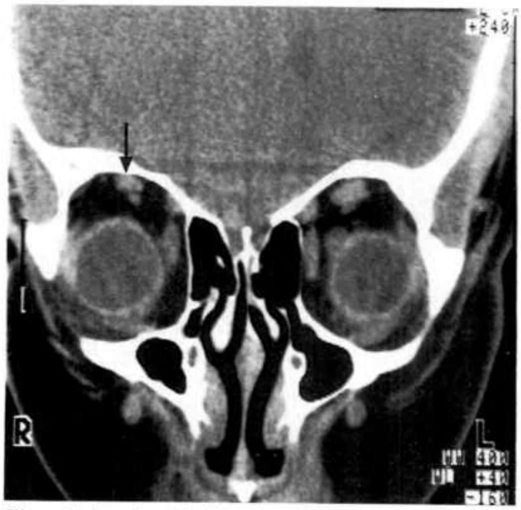


Figure 2: Atrophy of the levator and superior rectus muscles of the right eye on coronal CT scan (arrow).

without atrophy.[11] Spontaneous filtration[4] and asymmetric pigmentary glaucoma[9] have been described, and central vein occlusion may also occur.[12] Atrophy of the skin in the periorbital region results in abnormality of the shape of the eyelid and loss of hair of the eyebrow and cilia.[4 7 9 13] Motility disturbances have also been reported,[4 9 14] and two of these were accompanied by involvement of the levator muscle, resulting in ptosis.[9 14] CT scanning of the orbit has been described in two cases, but no muscle involvement was found.[7 14]

To our knowledge our case is the first one described in which muscle involvement is demonstrated by CT-scanning. Surgical correction of ptosis has been performed on one patient,[9] with a recurrence of the ptosis after 12 years. In our case the ptosis recurred twice, about two years after surgical correction. An explanation for the recurrence could be that scleroderma en coup de sabre which has its onset during childhood, progresses slowly.[15]

This case illustrates that if ptosis recurs after surgical correction, especially when it is accompanied by skin lesions or motility disturbances, one should consider the diagnosis scleroderma en coup de sabre.

1 Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KE, eds *Dermatology in general medicine* New York McGraw-Hill, 1987· 1841–52
2 Duke-Elder S, MacFaul PA *System of ophthalmology* London Kimpton, 1974· 13: 330–4
3 Coyle EF Scleroderma of the cornea. *Br J Ophthalmol* 1956, 40: 239–41
4 Gerke E, Meyer-Schwickerath G, Joussen F Sclerodermie en coup de sabre mit spontaner Filterkissenbildung *Klin Monatsbl Augenheilkd* 1976; 168: 426–8
5 Franceschetti A, Jadassohn W, Paillard R, Hofer R, Golay M. Hémiatrophie faciale ou sclérodermie en coup de sabre *Dermatologica* 1958, 116: 331
6 Sugar HS, Banks TL Fuchs heterochromic cyclitis associated with facial hemiatrophy (scleroderma en coup de sabre) *Am J Ophthalmol* 1964, 57: 627–32
7 Serup J, Alsbirk PH Localized scleroderma en coup de sabre and iridopalpebral atrophy at the same line *Acta Derm Venereol (Stockh)* 1983, 106. 75–7
8 Perkins ES Heterochromic uveitis *Trans Ophthalmol Soc UK* 1961, 81: 53–66
9 Stone RA, Schei HG Periorbital scleroderma associated with heterochromia iridis *Am J Ophthalmol* 1980, 90· 858–61
10 Segal P, Jablonaka S, Mrzyglod S Ocular changes in linear scleroderma *Am J Ophthalmol* 1961, 51 807–13
11 Tang RA, Mewis-Christmann L, Wolf J, Wilkin RB Pseudo oculomotor palsy as the presenting sign of linear scleroderma *J Pediatr Ophthalmol Strabismus* 1986; 23: 236–8
12 Josten K Sclerodermie en coup de sabre und Auge *Klin Monatsbl Augenheilkd* 1958, 133: 567–70
13 Olver J, Laidler P Acquired Brown's syndrome in a patient with combined lichen sclerosus at atrophicus and morphoea *Br J Ophthalmol* 1988, 72: 552–7
14 Serup J, Serup L, Sjo O Localized scleroderma 'en coup de sabre' with external eye muscle involvement at the same line *Clin Exp Dermatol* 1984, 9. 196–200
15 Curtis AC, Jansen TG. The prognosis of localized scleroderma *Arch Dermatol* 1958, 78: 749–56

British Journal of Ophthalmology, 1990, 74, 696–697

Homocystinuria presenting as central retinal artery occlusion and longstanding thromboembolic disease

W v d Berg, F D Verbraak, P J M Bos

Abstract

A case of central retinal artery occlusion in a patient with a 10-year history of unexplained thromboembolic disease due to a secondary hypercoagulable state is presented. Ophthalmological examination led to the final diagnosis.

Central retinal artery occlusion is a devastating ophthalmological event leading to severe impairment of vision. It may be associated with life threatening systemic diseases. Causes of it include embolism (from the heart or carotid arteries), vaso-obliteration (due to either atheroma or arteritis), or a high extravascular pressure (due to high intraocular pressure as in acute glaucoma or excessive pressure on the globe during surgery).[1][2] Though the cause of the occlusion is not always identified, the clinical picture (hyperacute profound loss of vision, afferent pupillary defect, oedematous retina with a cherry red spot at the site of the fovea) is easy to recognise.

The ophthalmologist usually has a modest contribution in the identification of the underlying cause of the arterial occlusion. In this paper a case is presented in which the ophthalmologist led the way to the correct diagnosis.

Case report

A 31-year-old woman, with a long and slender habitus, presented to an ophthalmologist with sudden visual loss of the right eye four days after premature delivery of a child. She had a 10-year history of unexplained recurrent thromboembolic disease comprising deep venous thrombosis at the age of 19 years followed by three periods of severe arterial insufficiency of the iliac arteries leading to difficulty in walking. The first of these attacks appeared spontaneously and the following two coincided with her pregnancies. She was consequently on phenprocoumon derivatives. During her pregnancies these were replaced by subcutaneous heparin two weeks before delivery. The family history was negative with respect to ophthalmological abnormalities or thromboembolic disease.

Her visual acuity in the right eye was counting fingers, and in the left 2/5 (8/20) (with S-4). Both eyes showed a normal cornea. Iridodonesis was present and a subluxation of the lens was noted in both eyes. The intraocular pressures were normal.

On ophthalmoscopy the right eye showed a pale optic disc, narrow irregular arteries, and retinal oedema in the posterior pole, with a cherry red spot. The left eye showed no abnormalities. The ophthalmologist diagnosed a central retinal artery occlusion in the right eye in a patient with the Marfan's syndrome, together with an unexplained thromboembolic disorder.

For further evaluation of the vascular disorder she was referred to the department of internal medicine of the Academic Medical Centre in Amsterdam, where she was seen by one of the authors (WVB). Her visual acuity in the right eye was still counting fingers and in the left 4/5 (16/20) (with S-8). The lenses were noted to be spherical, which explained the increased myopia, and were displaced inferonasally. The intraocular pressure in both eyes was 15 mmHg, with negative pupillary block provocation tests (measurements after mydriatics and in the prone position). Ophthalmoscopy confirmed the presence of a central retinal artery occlusion in the right eye.

The finding of a subluxation of the lens in this patient with an extensive history of arteriovenous thrombosis suggested the diagnosis of homocystinuria rather than the Marfan syndrome. Biochemical analysis confirmed the diagnosis of homocystinuria, and the return to normal of the abnormal values after administration of pyridoxine proved this to be caused by a vitamin B6 responsive cystathionine-β-synthetase deficiency.

The final diagnosis, after 10 years of recurrent thromboembolic disease, was vitamin B6 responsive homocystinuria, an autosomal recessive disorder due to cystathionine-β-synthetase deficiency: a treatable disorder. Six months after initiation of high doses of pyridoxine therapy (750 mg/ per day) she was free of complaints due to arterial insufficiency, except for the permanent loss of vision in her right eye.

Discussion

Recurrent deep venous thrombosis and multiple arterial occlusions are symptoms of a hypercoagulable state. Primary hypercoagulable states are defined by a defect in the physiological anticoagulant mechanism (for example, AT III deficiency, protein C and/or protein S deficiency). Secondary hypercoagulable states are disorders in patients with underlying systemic diseases or clinical conditions known to be associated with an increased risk of thrombosis, such as malignancy, hyperviscosity syndromes, diabetes mellitus, pregnancy, and the use of oral contraceptives.[3]

In our patient, during her 10-year history of thromboembolic disease, aggravated by two pregnancies, the exact cause of her hypercoagulable state was never identified despite extensive investigations. Sudden visual loss of the right eye brought her to the ophthalmologist, who found a central retinal artery occlusion

Department of Ophthalmology, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
W v d Berg
F D Verbraak
P J M Bos

Correspondence to: Dr P J M Bos.

Accepted for publication 31 May 1990

without local predisposing factors and an ectopia lentis. Though at first the Marfan syndrome was suspected, the correct diagnosis of homocystinuria was finally made.

Homocystinuria is an autosomal recessive inborn error of metabolism which is most commonly due to reduced activity of the enzyme cystathionine-β-synthetase.[4,5] There is considerable variation in the degree of expression of the genetic defect and therefore in the number and severity of clinical complications. At one extreme patients may present with dislocated lenses, severe skeletal abnormalities, mental retardation, and vascular occlusions, whereas others, detected at early screening or a family investigation, have virtually no clinical abnormalities.[6] Examination of this patient's family, including both her children, revealed no other cases of homocystinuria.

Ectopia lentis is present in 92% of untreated patients above the age of 20 years. Clinically the existence of a dislocated lens presents itself with increased myopia and/or iridodonesis, as in this patient. Other ophthalmological features are microcystic peripheral retinal degeneration, secondary pupillary block glaucoma, and retinal detachment.[4,7]

The long and slender habitus frequently encountered in patients with homocystinuria together with ectopia lentis may erroneously lead to a diagnosis of the Marfan's syndrome. The direction of the dislocation of the lens, in Marfan's syndrome upwards and/or temporal and in homocystinuria downwards and/or nasal, is indicative but cannot be considered diagnostic.[8]

There is a 40% probability that patients with homocystinuria will have a thromboembolic lesion in the first 20 years of their life.[6] Multiple arterial occlusions in a patient with homocystinuria – being one of the secondary hypercoagulable states – associated with pregnancy has been described.[9] A central retinal artery occlusion can be expected to occur in homocystinuria as a consequence of this hypercoagulable state. Surprisingly this dramatic event has been recorded only twice, and in both cases there were local predisposing factors.[10,11] One case report describes a boy of 6 years old who developed central retinal artery occlusion after an attack of bilateral acute glaucoma caused by his luxated lenses. The other case was of thrombosis of the retinal artery after surgical removal of dislocated lenses. Our patient never underwent eye surgery, and secondary pupillary block glaucoma seemed highly unlikely in view of the negative provocation tests.

Treatment consists of administration of pyridoxine in pharmacological amounts or, in pyridoxine non-responders, a methionine-restricted diet with supplementation of L-cysteine. Sometimes a combination of both regimens is given. In patients who have been adequately treated no thromboembolic episodes have been reported. Treatment does not seem to influence the occurrence or the course of the lens subluxation.[6,11,12]

Conclusions

In all cases of ectopia lentis a biochemical screening for homocystinuria seems mandatory. This case provides a strong argument to do the same in cases of patients who have a severe secondary hypercoagulable state at a young age with no recognisable predisposing factors. The combination of ectopia lentis and thromboembolic disease, an almost pathognomonic combination of symptoms, makes screening an absolute necessity.

To our knowledge this is the first report of a patient with homocystinuria and central retinal artery occlusion without local predisposing factors. This raises the question whether patients presenting with a central retinal artery occlusion at a young age should be screened for homocystinuria as a routine.

1 Karjalainen K Occlusion of the central retinal artery and retinal branch arterioles. a clinical, tonographic and fluorescein angiographic study of 175 patients *Acta Ophthalmol (Kbh)* 1971, 109: (suppl) 1–95.

2 Brown GC, Magargal LE, Shields JA, Goldberg RE, Walsh PN. Retinal arterial obstruction in children and young adults. *Ophthalmology* 1981; 88: 18–25.

3 Schafer AI The hypercoagulable states *Ann Intern Med* 1985; 102: 814–28

4 Burke JP, O'Keefe M, Bowell R, Naughten ER Ocular complications in homocystinuria – early and late treated. *Br J Ophthalmol* 1989; 73: 427–31

5 Boers GHJ, Polder TW, Cruysberg JRM, *et al.* Homocystinuria versus Marfan's syndrome: a therapeutic relevance of the differential diagnosis. *Neth J Med* 1984, 27: 206–12.

6 Mudd SH, Skovby E, Levy HL. The natural history of homocystinuria due to cystathionine-beta-synthetase deficiency *Am J Hum Genet* 1985; 37: 1–31.

7 Ramsay MS, Yanoff M, Fine BS. The ocular histopathology of homocystinuria. *Am J Ophthalmol* 1972, 74: 377–85

8 Cross HE, Jensen AD Ocular manifestations in the Marfan syndrome and homocystinuria *Am J Ophthalmol* 1973, 75: 405–20

9 Newman G, Mitchell JR. Homocystinuria presenting as multiple arterial occlusions. *Q J Med* 1984, 210: 251–8

10 Wilson RS, Ruiz RS. Bilateral central retinal artery occlusion in homocystinuria *Arch Ophthalmol* 1969, 82: 267–8

11 Groebe H. Homocystinuria (cystathionine synthetase deficiency). Results of treatment in late-diagnosed patients. *Eur J Pediatr* 1980; 135: 199–203

12 Schuh S, Rosenblatt DS, Cooper BA, *et al* Homocystinuria and megaloblastic anemia responsive to vitamin B12 therapy *N Engl J Med* 1984; 310: 686–90

British Journal of Ophthalmology, 1990, **74**, 698–699

Chickenpox chorioretinitis

S P Kelly, A R Rosenthal

Abstract

Chickenpox infection in an adult was complicated by peripheral chorioretinitis and treated with oral acyclovir. Similarities of this case to the recently proposed mild type of acute retinal necrosis syndrome are discussed.

A 27-year-old woman presented with a short history of floaters and blurring of vision in the right eye. Both the patient and her 3-month-old infant had had typical varicella infection in the previous two weeks. She had symptoms of recent sore throat, pyrexia, headache, and varicella vesicular eruption on the trunk.

The visual acuity was 6/6 Snellen in both eyes. There was 1+ external injection in the right eye. The intraocular pressures were normal. In the right anterior chamber 1+ cells were present, with inferior keratic precipitates. There were 2+ posterior vitreous cells in the right eye. Multiple areas of active yellow-grey foci of chorioretinitis (Fig 1) were present throughout 360° of the peripheral fundus in the right eye. Perivasculitis (Fig 2) was also noted. The left eye was normal.

Typical varicella eruption was present on the back and abdomen. Petchiae were visible in the pharynx. Varicella complement fixation tests were strongly positive. All other serological and immunological studies gave normal results.

Topical steroids and mydriatics were prescribed. Because of an impression of progression of the clinical signs during the second week, with the development of additional yellow-white exudates in the peripheral fundus, which became confluent (Fig 3), acyclovir 200 mg four times daily was prescribed orally for seven days. One month later the anterior chamber was quiet and the peripheral lesions had become scarred, with localised retinochoroidal atrophy and secondary

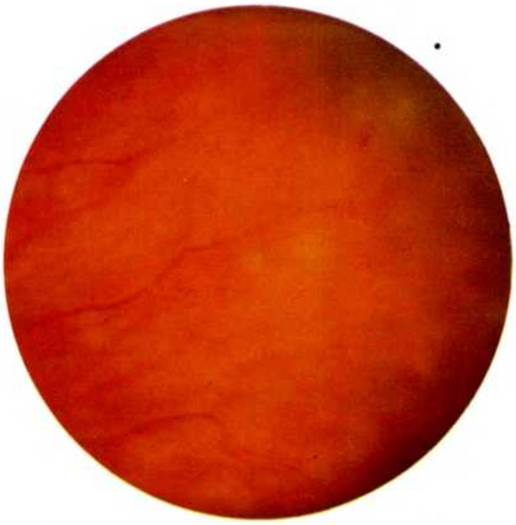


Figure 1 Foci of active chorioretinitis in peripheral fundus.

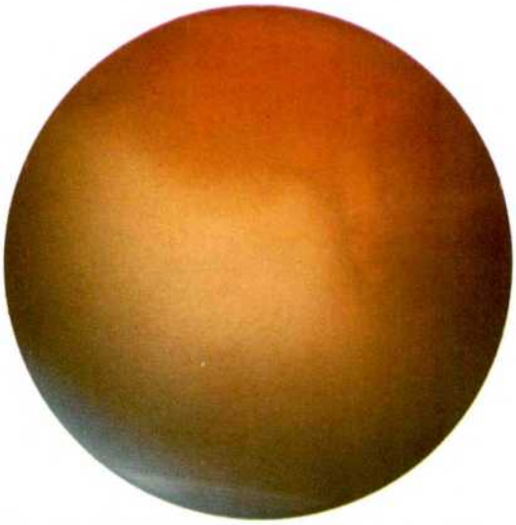


Figure 3 Progression of exudates, which became confluent.

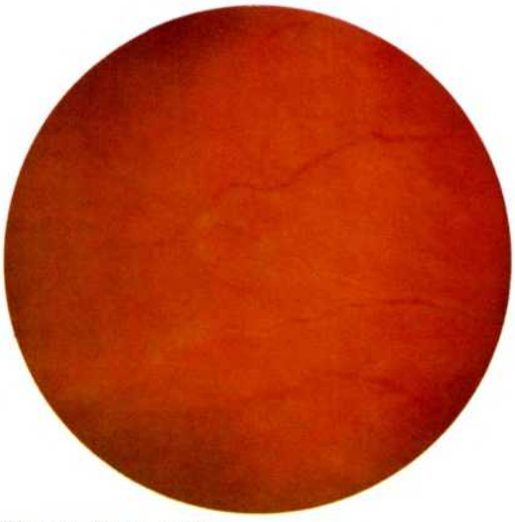


Figure 2 Perivasculitis.

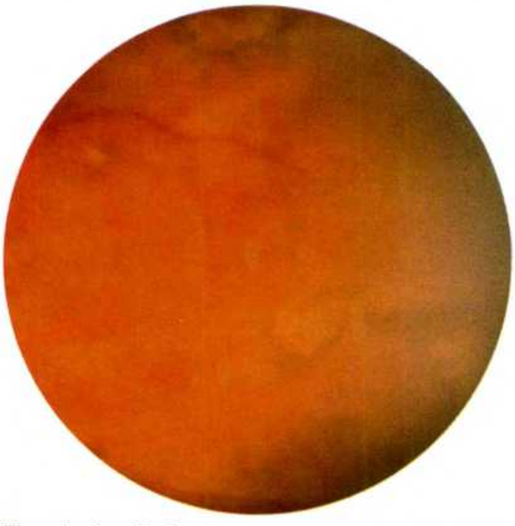


Figure 4 Localised retinochoroidal atrophy in areas where foci of chorioretinitis previously existed.

Manchester Royal Eye Hospital
S P Kelly

University of Leicester
A R Rosenthal

Correspondence to:
Mr Simon Kelly, Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH.

Accepted for publication
11 April 1990

retinal pigment epithelial changes evolving (Fig 4). No retinal breaks occurred.

Discussion

Varicella-zoster virus (VZV) is a ubiquitous human infection, producing chickenpox in children and zoster in adults. While the ophthalmic manifestations of herpes zoster are well recognised, ocular complications of varicella (chickenpox) are rare. Second attacks of chickenpox are most unusual, as immunity is lifelong. Only 1·8% of cases of chickenpox occur after the second decade of life and then produce more severe systemic illness than in children.[1]

Vesicular lid lesions or conjunctivitis and occasionally corneal involvement occur in 4% of unselected cases of chickenpox.[2,3] Other ocular manifestations are unusual and have included canalicular obstruction,[4] anterior uveitis,[3,5] cataracts,[6] optic neuritis,[7] and optic disc pigmentation.[8] Extraocular muscle palsies,[9] internal ophthalmoplegia,[10] and central nervous system disorders ranging from aseptic meningitis to fulminating encephalitis occur.[11] One in 1000 cases of varicella involve the central nervous system clinically.[11] There is one other report of involvement of the retina or choroid in acute chickenpox infection: bilateral optic neuritis and a macular lesion resembling 'chorioretinal atrophy' occurred during varicella encephalitis in an infant.[12]

Choroiditis has been described with herpes zoster ophthalmicus.[13]

Matsuo and associates recently described a mild type of acute retinal necrosis syndrome.[14] Six patients developed peripheral retinal exudates which progressed gradually to the posterior pole without causing retinal detachment. In three patients antibody to VZV was found in the aqueous humour. One patient had developed varicella eruption with peripheral retinal exudates in late pregnancy and was treated with prednisolone and acyclovir intravenous infusions post partum.[15] Our patient's peripheral fundus signs resembled the Japanese findings and thus may have also exhibited a mild form of the acute retinal necrosis syndrome. The agent responsible for acute retinal necrosis syndrome may be a mutant strain of VZV with a predilection for the retina.[16,17]

Specific antiviral treatment, or interferon, is indicated when varicella infection occurs in immunocompromised patients.[18] In view of the progressive nature of the chorioretinitis we considered acyclovir was indicated in our patient. Matsuo and colleagues' six patients were treated with high doses of systemic steroids, with the addition of acyclovir in four cases.[14]

The peripheral fundus should be examined in varicella patients with visual symptoms, and any further cases of mild acute retinal necrosis syndrome identified should be reported.

We thank the Wellcome Foundaton Ltd for assistance with publication costs

1 Centres for disease control Chickenpox in the United States, 1972–77 *J Infect Dis* 1979, 140. 257–60

2 Griffin WP, Searle CWA Ocular manifestations of varicella *Lancet* 1953, ii 168–9.

3 Jordan DR, Leon-Paul N, Clarke WN Ocular involvement in varicella *Clin Pediatr* 1983, 23. 434–6

4 Sanke RF, Welham RAN Lacrimal canalicular obstruction following chickenpox *Br J Ophthalmol* 1982, 66: 71–4

5 Edwards TS Ophthalmic complications from varicella *J Pediatr Ophthalmol Strabismus* 1965, 2 37–40

6 Robb RM. Cataracts following varicella infection *Arch Ophthalmol* 1972, 87: 352–4

7 Purvin V, Hrisomalos N, Dunn D. Varicella optic neuritis *Neurology* 1988, 38 501–3

8 Taylor DSI, ffytche TJ Optic disc pigmentation associated with a field defect following chickenpox *J Pediatr Ophthalmol Strabismus* 1976; 13: 352–4

9 Sharf B, Hyams S Oculomotor palsy following varicella *J Pediatr Ophthalmol Strabismus* 1972, 9 347–50

10 Dubois HF, van Bijsterveld OP Internal ophthalmoplegia, an uncommon complication of varicella, a common infection *Ophthalmologica* 1977; 175· 263–8

11 Ho DD, Hirsch MS Acute viral encephalitis *Med Clin North Am* 1985; 69: 415–29

12 Copenhaver RM Chickenpox with retinopathy *Arch Ophthalmol* 1966; 75: 199–200.

13 Amano Y, Ohashi Y, Haruta Y, Kinoshita S, Tano Y, Manabe R A new fundus finding in patients with zoster ophthalmicus *Am J Ophthalmol* 1986, 102: 532–3

14 Matsuo T, Nakayama T, Koyama T, Koyama M, Matsuo N. A proposed mild type of acute retinal necrosis syndrome *Am J Ophthalmol* 1988, 105. 579–83

15 Matsuo T, Ohno A, Matsuo N. Acute retinal necrosis syndrome following chickenpox in a pregnant woman *Jpn J Ophthalmol* 1988, 32. 70–4

16 Culbertson WW, Blumenkranz MS, Haines H, Gass JDM, Mitchell KB, Norton EWD The acute retinal necrosis syndrome Part II Histopathology and etiology *Ophthalmology* 1982, 89: 1317–25

17 O'Connor GR Endogeneous uveitis Part I Infectious entities In. Kraus-Mackiw E, ed *Uveitis, pathophysiology and therapy* 2nd ed New York Thieme, 1986 47–74

18 Brunell PA Varicella-zoster infections In Fegin RD, Cherry JD. eds *Textbook of pediatric infectious diseases* Philadelphia Saunders, 1987 1602–7

British Journal of Ophthalmology, 1990, 74, 700–701

Choroidal osteoma (osseous choristoma): an atypical case

G Cennamo, G Iaccarino, G de Crecchio, G Liguori

Abstract

A case of choroidal osteoma presenting in a 22-year-old girl is reported. The tumour, unilateral and in a juxtapapillary site, appeared markedly elevated on the retinal plane, not flat or slightly elevated as in previous reports. Visual acuity was not affected, and there was a complete absence of subjective symptoms. Echography, fluorangiography, computerised tomography, and visual field tests were performed. Echography is the best method for identifying and differentiating this lesion from a malignant tumour.

Choroidal osteoma, or osseous choristoma, was first described by Gass *et al* in 1978.[1] It is usually present from birth and typically has a low development potential. It presents unilaterally in most cases, has a predilection for the female sex, and favours a juxtapapillary location, becoming clinically manifest when it involves the macula. It is usually diagnosed during the second and third decades of life.[2]

Ophthalmoscopy shows a circumscribed, irregularly ovoid or round mass with defined borders. The colour is related to the degree of thinning and depigmentation of the overlying retinal pigment epithelium,[3] varying from a diffuse reddish orange, thus resembling choroidal haemangioma, to a yellowish white coloration which gradually shades peripherally into pinkish yellow, becoming indistinguishable from the surrounding healthy area.[4]

We report here a case of choroidal osteoma which, because of its atypical features, presented particular diagnostic problems.

Università degli Studi di Napoli, I Facoltà di Medicina e Chirurgia, Istituto di Clinica Oculistica
G Iaccarino

II Facoltà di Medicina e Chirurgia
Istituto di Oftalmologia
G Cennamo
G de Crecchio
G Liguori

Correspondence to:
Professor G Cennamo, Clinica Oculistica, II Policlinico, via Pansini 5, Napoli, Italy.

Accepted for publication
22 March 1990

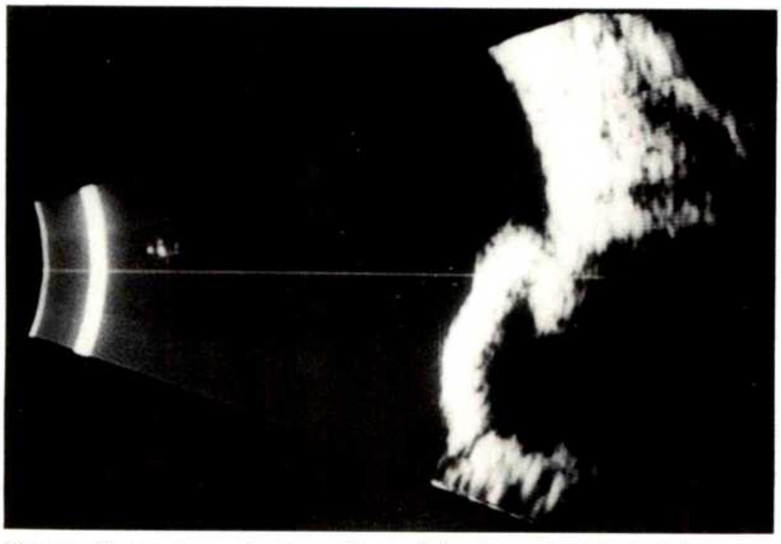


Figure 2 B-scan echogram showing a solid mass lesion of extremely high reflectivity shadowing all the structures behind it.

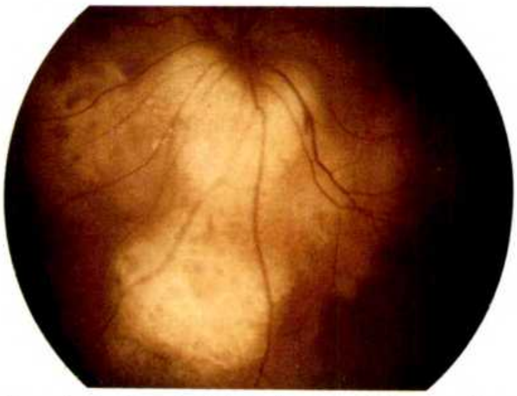


Figure 1 Left eye. A solid mass located in the juxtapapillary region of the lower nasal quadrant. The mass had a yellowish white centre and was elevated from the retinal plane.

Case report

A 22 year-old-girl presented without any previous relevant medical history. The right eye was normal. In the left eye the visual acuity was 60/60 and the anterior segment normal. A fundus examination revealed a solid mass of approximately 6×6 papillary diameters located in the juxtapapillary region of the lower nasal quadrant. The mass was elevated from the retinal plane by about 5 dioptres and had a yellowish white centre and pinkish yellow sloping edges (Fig 1). Standardised echography[5] showed the lesion as a solid, raised subretinal mass with an extremely high reflectivity, observable even at the anterior surface of the lesion and shadowing the sclera and also the posterior orbital tissues[6] (Fig 2). The echographic images of the lesion were of foreign body type, showing spikes of extremely high reflectivity from the retinal surface corresponding to the tumour site (Fig 3). In the remaining areas the thickness of the retina and choroid was normal; the optic nerve was also of normal diameter and reflectivity.

Fluorescein angiography showed a pattern of irregular hyperfluorescence overlying the tumour and evidence of diffuse staining of the tumour surface during the later stages. Numerous capillaries on the surface of the choroidal osteoma were present in the early phase of the angiogram (Fig 4). CT showed a radiodense lesion adjacent to the left optic nerve head, at the posterior pole, of the same density as normal bone (Fig 5).

When the patient was seen a year after the first observation, no variations of the mass were noted.

Discussion

The 5 dioptres elevation from the plane renders this case atypical. The clinical picture of this tumour – its location, unilaterality, its arising from a single focus, and the patient's age when it

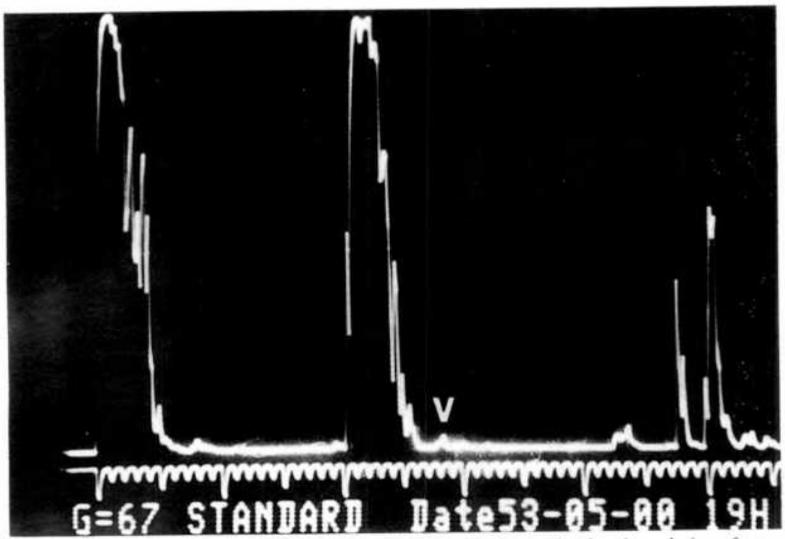


Figure 3 Echogram obtained with standardised A-scan echography showing a lesion of very high reflectivity and posterior shadowing due to the presence of bone tissue in the choroidal layer. The arrow indicates a very low spike obtained from the outer sclera.

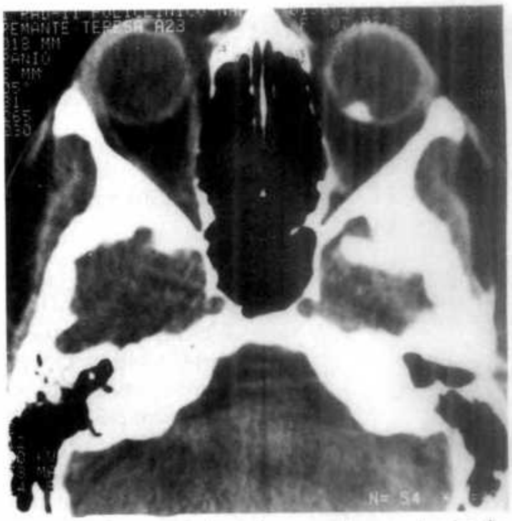


Figure 5 Computerised axial tomography scan showing the presence of a bony plaque in the juxtapapillary region adjacent to the left optic nerve head.

was first observed facilitated its diagnostic differentiation from metastatic carcinoma, poorly pigmented malignant choroidal melanoma, optic nerve tumours involving the posterior pole of the eye, choroid ossification (typical of the phthisical eye), retinoblastoma, and choroid haemangioma. But it is echography that allows an exact differential diagnosis to be made. Ultrasonically osteoma presents as a solid mass with a single spike of extremely high reflectivity which is not spontaneously mobile, with marked acoustic shadowing of the tissue behind the lesion.

Ultrasonically malignant melanoma presents with a regular, medium to low reflectivity with sudden rapid, spontaneous movements of the spikes indicating the presence of abnormal vascularisation. In contrast, the reflectivity of the metastatic carcinoma is medium to high and irregular, and spontaneous movements of the spikes are absent. With both these lesions, when shadowing of the posterior orbital tissues is present it is never so pronounced as it is in osteoma. The presence of a normal optic nerve with standardised A scan rules out the presence of a primitive neoplastic tumour of this structure.[7]

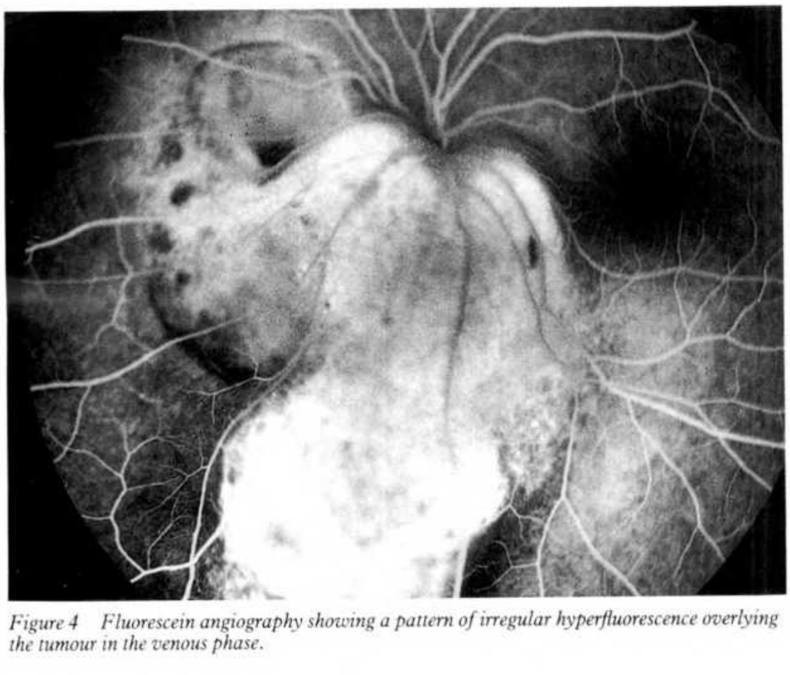


Figure 4 Fluorescein angiography showing a pattern of irregular hyperfluorescence overlying the tumour in the venous phase.

Ossification of the choroid is typical of the phthisical eye. The phthisical eye, because of increased thickness and folds of the choroid, shows a shadowing of the posterior orbital tissues. Moreover this shadowing may be due to calcification of the choroid, which is present in a very advanced stage of the disease and distributed in a mottled fashion, not in a single mass as in osteoma. In retinoblastoma, in contrast to choroid osteoma, there is no single spike of high reflectivity of foreign body type but rather a series of spikes of high reflectivity originating both from the surface and from the neoplastic mass. These are referable to the presence of irregularly distributed calcification inside the tumour.[8]

In conclusion, owing to clinical similarities with osteoma serious problems of differential diagnosis are encountered with calcified haemangioma of the choroid. CT and echography makes identification and differentiation of osteoma and calcified haemangioma possible. Osteoma presents as a single, compact, calcified mass, while calcified haemangioma presents as bone surrounded by many large vascular channels.[9]

1 Gass JDM, Guerry RK, Jack RL, Harris C. Choroidal osteomas. *Arch Ophthalmol* 1978; **96:** 428–35.
2 Baum M, Pinkerton AR, Berler DK, Kramer KK. Choroidal osteomas. *Ann Ophthalmol* 1979; **11:** 1849–51.
3 Mc Leod BK. Choroidal osteomas presenting in pregnancy. *Br J Ophthalmol* 1988; **72:** 612–4.
4 Gass JDM New observations concerning choroidal osteomas. *Int Ophthalmol* 1979; **1:** 71–84.
5 Ossoinig KC. In: Dallow CRL, ed. Standardised echography: basic principles, clinical applications and results in ophthalmic ultrasonography: comparative techniques *Int Ophthalmol Clin* 1979; **19:** 127.
6 Santoni G, Ricci AL, Lupidi G, Ciorba E, Fiore C. Choristome osseux de la choroide bilateral et microphtalmie asymetrique. *J Fr Ophtalmol* 1988; **11:** 363–7.
7 Ossoinig KC, Cennamo G, Frazier-Byrne S. Echographic differential diagnosis of optic nerve lesion. *Doc Ophthalmol Proc Ser* 1981; **29:** 327–32.
8 Ossoinig KC, Cennamo G, Green RL, Weyer SML. Echographic results in the diagnosis of retinoblastoma. *Doc Ophthalmol Proc Ser* 1981; **29:** 103–7.
9 Reese AB. *Tumours of the eye.* 3rd ed. New York: Harper and Row, 1976: 266–7.

British Journal of Ophthalmology, 1990, 74, 702–703

Lobular pattern of choriocapillaris in pre-eclampsia with aldosteronism

Yoshihiro Saito, Tatsuya Omoto, Masakatsu Fukuda

Department of Ophthalmology, Osaka University Medical School, Japan
Y Saito

Department of Ophthalmology, Kansai Rosai Hospital, Osaka, Japan
T Omoto

Department of Ophthalmology, Osaka Teishin Hospital, Japan
M Fukuda

Correspondence to:
Yoshihiro Saito, MD,
Department of Ophthalmology, Osaka University Medical School, 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan.

Accepted for publication
23 May 1990

Abstract

We report a case of geographic or mosaic pattern yellowish opaque foci in the left eye of a 36-year-old woman who suffered from severe pre-eclampsia. Though the geographic lesions resulted in chorioretinal atrophy, the mosaic lesion led to no significant atrophy. These two findings were both diagnosed as manifestations of choroidal ischaemia, the former due to choroidal artery occlusion, the latter to transient insufficiency of choroidal circulation, which reflects the lobular pattern of the choriocapillaris.

Patients with pre-eclampsia sometimes suffer from ocular complications, which are believed to arise mainly from retinal or choroidal vascular disorder. As to choroidal ischaemia in toxaemia of pregnancy,[1,2] serous retinal detachment and deep retinal yellowish opaque focus (YOF) are the most important findings. The present report is of a case of an uncommon manifestation of choroidal vascular disorder.

Case report

A 36-year-old woman (2 gravida, 2 para) complained of decreased vision in her left eye two days after pre-eclampsia necessitated caesarean section at 34 weeks of pregnancy. Her blood pressure was 200/110 mmHg, 24-hour urine protein 1750 mg/dl (10·4 mmol/24 h), with generalised oedema. The red blood cell count was 3200×10^9/l, white blood cell count 14·9×10^9/l and platelet count 105×10^9/l. The prothrombin time was 120% of normal, partial thromboplastin time 34 seconds, fibrinogen 4·3 g/l and fibrin degradative product 10 μg/l. Serum potassium was 2·8 mmol/l.

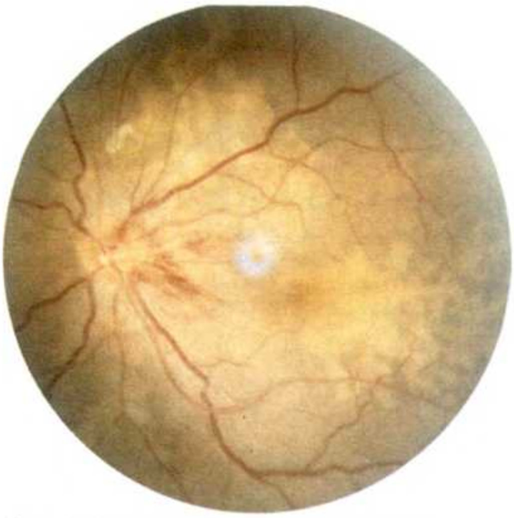


Figure 2 One week later, mosaic YOFs and retinal detachment have disappeared. Note peripapillary and temporal geographic YOFs. Central blue ring is an artefact.

At the first ophthalmological examination five days after delivery both fundi showed retinal angiospasm, flame-shaped retinal haemorrhages, cotton-wool patches, and papilloedema. In addition there were peripapillary and temporal macular geographic YOFs in the left posterior fundus at the level of the retinal pigment epithelium. Multiple isolated and some fused 1/4 disc diameter YOFs were also distributed in mosaic

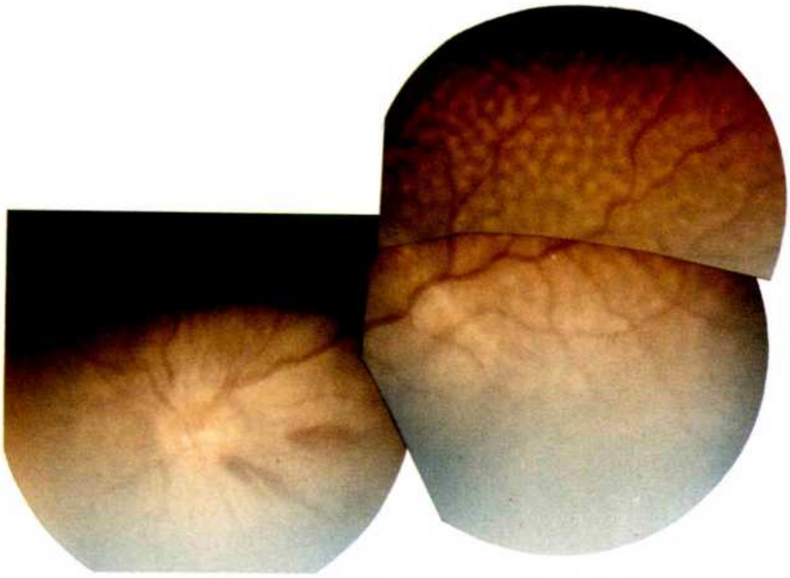


Figure 1 Left fundus at first ophthalmoscopic examination. Note peripapillary geographic yellowish opaque focus (YOF), mosaic YOFs in superotemporal area, and diffuse serous retinal detachment.

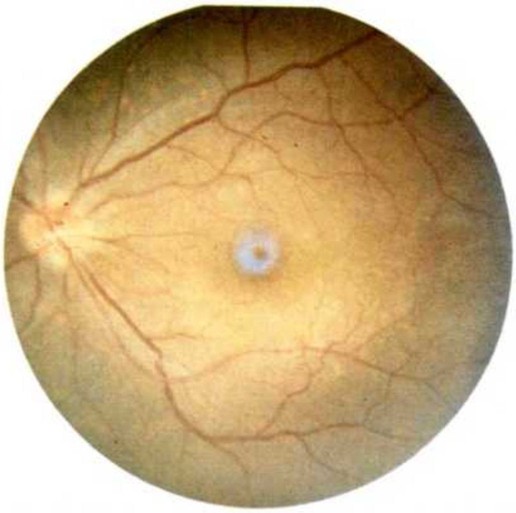


Figure 3 Three months later, chorioretinal atrophy appears at sites of previous geographic YOFs. Central blue ring is an artefact.

fashion throughout the superotemporal to mid-peripheral area (Fig 1). Furthermore, diffuse serous retinal detachment involved the macula. The visual acuity of the eye was finger counting at 1 m.

One week later, though the peripapillary and temporal geographic YOF remained, the mosaic YOFs and serous retinal detachment had disappeared (Fig 2). Fluorescein angiography was not performed at this time because of the patient's poor systemic condition.

Three months later chorioretinal atrophy was seen at the sites of the geographic YOFs but no scarring was visible ophthalmoscopically or angiographically at the sites of the mosaic YOFs (Fig 3). Visual acuity improved to 20/20. Computed tomography post partum revealed a left adrenal tumour. Partial adrenalectomy was performed. The diagnosis was primary aldosteronism due to a functional adenoma.

Discussion

In this case the geographic YOFs were thought to be caused by occlusion of a choroidal artery, as in the triangular syndrome. In addition the area of mosaic YOFs coincides with one of the frequent sites of choroidal atrophy in the triangular syndrome.[3] Since the unit size of the mosaic YOF is the same as that of the choriocapillaris,[4] these units are thought to be choroidal lobules. In the mosaic area units tend to fuse with each other, a condition presumed to be a precursor of geographic YOFs. Mosaic YOFs, which in the present case did not develop into choroidal atrophy, is also regarded as one of the manifestations of choroidal ischaemia. Presumably this mosaic YOF was not caused by a thrombosis within the choriocapillaris or by persistent occlusion of the choroidal artery. The authors speculate that such a pattern of YOFs seems to be caused by transient occlusion or spasm of the proximal choroidal artery. The presence of these two types of outcome of choroidal ischaemia in one eye provides clinical evidence of the segmental nature of the choroidal vasculature.[5]

1 Fastenberg DM, Fetkenhour CL, Choromokos E, *et al.* Choroidal vascular changes in toxemia of pregnancy. *Am J Ophthalmol* 1980; **89**: 362–8.

2 Saito Y. Retinochoroidal changes in toxemia of pregnancy with the relation to hypertensive retinopathy and choroidopathy. *Nippon Ganka Gakkai Zasshi* 1990; **94**: 748–55.

3 Takeda M. Fluorescein angiographic findings in 'idiopathic' triangular syndrome. *Folia Ophthalmol Jpn* 1978; **29**: 1629–38.

4 Hayreh SS. The choriocapillaris. *Graefes Arch Clin Exp Ophthalmol* 1974; **192**: 165–79.

5 Hayreh SS. Segmental nature of choroidal vasculature. *Br J Ophthalmol* 1975; **59**: 631–48.

LETTERS TO THE EDITOR

Compact field charts

SIR,—It is often difficult to assess field examinations. Fields are often in the wrong order and comparison between one field and another difficult because the examinations are often performed under different conditions.

For six years we have found it easier to record Friedman fields on one sheet of paper. This we have achieved by reducing three standard Clement Clarke Field Charts Cat. No. 530 4010 on a photocopier from 230 mm×210 mm to 210 mm×100 mm. We then photocopy these reduced charts together and at the same time make a double sided copy to give us six reduced field charts on one sheet of paper.

In this way we find it easier to achieve standardised conditions such as intensity of stimulus and the wearing of reading spectacles if needed. It is also easier to see definite changes from the first visit to up to six years later, thus avoiding, if possible, the all too frequent insidious loss of vision and field.

The charts were originally designed by A. Friedmann and are produced by Clement Clarke International Ltd.

MICHAEL D O'RIORDAN
Croydon Eye Unit,
33 Mayday Road,
Thornton Heath,
Surrey CR4 7XN

Diabetes and retinal function

SIR,—I refer to your leading article[1] concerning a paper on an investigation into retinal function in the diabetic eye.[2] 'The mysterious absence of abnormality where abnormality would be expected' is almost certainly due to the method used to investigate the visual fields. It should also be said that the number of papers on the subject is larger than the list of references indicates.

I have not reviewed the literature since 1969,[3] but even then there were references to scotomata in patients with diabetes.[4,5] There has been a much more recent study which the authors of the paper under discussion may not have seen.[6] The conclusions reached in this paper are similar to those reached in mine; scotomata are common in diabetic eyes and are possibly due to microangiopathy.

It is puzzling that Bek and Lund-Andersen failed to find visual field defects in view of the fact that they used the same apparatus as the authors of the most recent study.

J A ROTH
3 Clevedon Drive,
Earley,
Reading,
Berkshire RG6 2XF

1 Smith RJH. Diabetes and retinal function. *Br J Ophthalmol* 1990; **74:** 385.
2 Bek T, Lund-Andersen H. Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy, *Br J Ophthalmol* 1990; **74:** 388–92.
3 Roth JA. Central visual field in diabetes. *Br J Ophthalmol* 1969; **53:** 16–25.
4 Dubois-Poulsen A. *Le champ visuel.* Paris: Masson, 1952: 654.
5 Lakowski R, Aspinall P. *The visual laboratory.* Edinburgh: 1966.
6 Trick GL, Trick LR, Kilo C. Visual field defects in patients with insulin-dependent and noninsulin-dependent diabetes. *Ophthalmology* 1990; **97:** 475–82.

•

SIR,—The paper presents parts of a systematic, comparative study of retinal morphology and neurosensory function in diabetic retinopathy. The authors employ a newly developed technique for accurate superimposition of visual field data on to the corresponding fundus morphology.[1] With this comparative technique scotomata have been found, which indicate that the loss of neurosensory function in diabetic retinopathy in many cases, but not always, may be ascribed to retinal microangiopathy. The authors' tentative explanation of this inconsistency is that impaired supply of deeper retinal layers, such as choroidal vascular impairment or pigment epithelial dysfunction, may be involved with other factors in producing visual loss in diabetic retinopathy. These findings, and also findings that confirm the results of Roth[2] will be published later.

Since 1969 several papers have been published on computerised perimetric studies of diabetic retinopathy, as for example Trick *et al*[3] However, to our knowledge the standard stimulus conditions developed for glaucoma screening (Goldmann stimulus size III combined with a stimulus spacing of 4·2 or 8·4 degrees) have been employed in all these studies. Except for proliferative diabetic retinopathy, where the scotomata to be found may be expected to be large,[4] these parameters are in our experience unsuitable for the detection of most of the small visual field scotomata characteristic of diabetic retinopathy. My colleagues and I have studied the influence of different perimetric stimulus variables on the ability to detect small scotomata,[5] and we have established that, besides a properly chosen small stimulus spacing, the stimulus size has to be chosen as small as possible. Therefore the most optimal parameters available on the Humphrey Field Analyzer (HFA) were chosen by combining Goldmann stimulus size I with a stimulus spacing of 1°. We believe that much important information has been lost in prior studies due to improper stimulus conditions, and due to the fact that a precise correlation between visual field data and the corresponding retinal morphology rarely has been made.

TOKE BEK
Department of Ophthalmology,
University of Copenhagen,
Gentofte Hospital,
2900 Hellerup, Denmark

1 Bek T, Lund-Andersen H. Accurate superimposition of visual field data onto fundus pictures. *Acta Ophthalmol (Kbh)* 1990; **68:** 11–8.
2 Roth JA. Central visual field in diabetes. *Br J Ophthalmol* 1969; **53:** 16–25.
3 Trick GL, Trick LR, Kilo C. Visual field defects in patients with insulin-dependent and noninsulin-dependent diabetes. *Ophthalmology* 1990; **97:** 475–82.
4 Bek T. Coexistence of localized scotomata and neovascularizations in proliferative diabetic retinopathy. *Acta Ophthalmol (Kbh)* 1990; **68:** 21–7.
5 Bek T, Lund-Andersen H. The influence of stimulus size on perimetric detection of small scotomata. *Graefes Arch Clin Exp Ophthalmol* 1989; **227:** 531–4.

FIFTY YEARS AGO

Annotation: The Journal in 1940

When the War came last year it was obvious that some curtailment in the size of the monthly numbers would have to be made, since the management could not foretell the financial position with any exactitude.

It is now possible to state that we shall be able to continue regular publication at any rate for this year, and every effort will be made to continue for the 'duration.' But the rationing system must continue, although it will be our aim to make this ration as large as possible. Papers dealing with war conditions will have priority over more ordinary material.

In these circumstances some delay in publishing papers is inevitable. We hope authors will bear this in mind and the Editors on their side will do their best to avoid undue delay.

Authors can help the Journal materially by keeping their proof corrections as low as possible. Manifest errors must of course be corrected, but there is no need to make endless corrections in the interests of the English language. The Editors feel that they can almost pardon a split infinitive in the cause of economy. And the writer has always had a sneaking sort of partiality for that old Kaiser Sigismund, who at the Council of Constance in 1414, was pulled up by one of the Cardinals on an obvious slip in grammar and replied 'I am King of the Romans and *super grammatician*.' It is so easy to make mistakes not only in professional matters but also in writing and speaking.

Br J Ophthalmol 1940; **24:** 189.

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- 24 hour delivery.
- Courier services.
- Personal delivery.

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia
Advancing The New Biology

A brighter start for dry eyes...

begins last thing at night

Used at night Lacri-lube soothes,
protects and lubricates dry eyes
for undisturbed sleep and
comfort on waking.

LACRI–LUBE®
petrolatum mineral oil **OINTMENT**

**At the end of the day
there's nothing quite like it
for dry eyes**

Lacri-Lube Prescribing Information. Presentation: Sterile, bland, non-medicated ophthalmic ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. **Uses:** Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. **Dosage and administration:** For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. **Contra-indications etc:** No known contra-indications. **Pharmaceutical precautions:** Store away from heat. To avoid contamination during use, do not touch tip to any surface. **Legal Category:** P. **Package quantities:** Available in 3.5g ophthalmic tubes. **Basic NHS Cost:** (as at May 1987) £1.76. **Product Licence Number:** PL 0426/0041. **Product Authorisation Number:** PA 148/38/1 (Allergan Pharmaceuticals (I) Limited, Westport, Co Mayo).

ALLERGAN PHARMACEUTICALS TM

SCIENCE WITH VISION

Allergan Limited.
High Wycombe, Bucks. HP12 3SH

Full prescribing information is available on request. ®denotes registered trademark

DECEMBER 1990 VOL 74 NO 12

197

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

705 Photic sneezes *Redmond Smith*

Original articles

706 Photic sneeze reflex in nephropathic cystinosis *Barrett Katz, Ronald B Melles, Michael R Swenson, Jerry A Schneider*

709 When is it safe to stop patching? *John G Oster, John W Simon, Paul Jenkins*

712 Peripheral contrast sensitivity in glaucoma and ocular hypertension *Fernando Falcão-Reis, Eamonn O'Donoghue, Rosaria Buceti, Roger A Hitchings, Geoffrey B Arden*

717 Precapsular film on the aging human lens: precursor of pseudoexfoliation? *Anthony J Dark, Barbara W Streeten*

723 Pathogenesis of corneal oedema associated with herpetic eye disease *William J O'Brien, Julie Guy, Jerry L Taylor*

731 Objective autorefraction in posterior chamber pseudophakia *Palaniswamy Sunder Raj, Tayo Akingbehin, Anthony M Levy*

734 Randomised single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery *C D G Jenkins, P J McDonnell, D J Spalton*

739 Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function *Michael F Marmor*

743 Diode laser trabeculoplasty (DLT) for primary open-angle glaucoma and ocular hypertension *Dominic McHugh, John Marshall, Timothy J ffytche, Peter A M Hamilton, Anthony Raven*

Case reports

748 Atraumatic iris cilia *G I S Mackintosh, M C Grayson*

750 Infectious mononucleosis presenting as bilateral acute dacryocystitis *P L Atkinson, A M Ansons, A Patterson*

751 Infestation of extraocular muscle by *Cysticercus cellulosae* *David A DiLoreto, Ross A Kennedy, Janet M Neigel, Jack Rootman*

753 **Index**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH JOURNAL OF OPHTHALMOLOGY

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE

Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Journal

COMMUNICATIONS Papers, which will be accepted on the understanding that they have not been and will not be published elsewhere and are subject to editorial revision, and books for review, should be addressed to the Editor, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Authors are asked to submit two copies of the text and references. Each author must sign the covering letter as evidence of consent to publication.

Reports of single cases are more likely to be accepted if restricted to 800 words plus essential references and illustrations.

ILLUSTRATIONS must be submitted in duplicate. Transparencies must be accompanied by prints. All must be labelled with the author's name, numbered in the same order as they are cited in the text irrespective of whether they are in colour or black-and-white, and have the top indicated. Lettering must be inserted by the author and be large enough for reproduction on the page. Radiographs must be submitted as prints. Stain used and a scale bar (or magnification) should be given. Legends must be typed on a separate sheet.

TABLES Each table should be on a separate sheet, have a heading, and contain no vertical rules.

REFERENCES In accordance with the Vancouver agreement references are cited by the numerical system. They must be *typed double spaced*.

References in the text must be cited in numerical order of first appearance. References in the list must be given in the numerical order in which they first appear in the text, not in alphabetical order of authors' names. References with one to six authors must include all authors' names; for references with more than six authors the first three should be given and then *et al*. Titles of journals should be abbreviated in accordance with the *Index Medicus* or given in full. References to books must include name of editor(s) if there is one, town where published, name of publisher, year, volume, page numbers. For examples see text.

References will not be checked in the editorial office. Responsibility for their accuracy and completeness lies with the author.

SI UNITS The work should be reported in the units used. If these were not SI units, the equivalent in SI units should be given in parentheses.

PROOFS Contributors will receive ONE proof, and should read it carefully for printers' errors. Alterations to the original text should be kept to a minimum and may be charged to the author.

REPRINTS may be ordered from the Publishing Manager when proofs are returned.

COPYRIGHT © 1990 by the *British Journal of Ophthalmology*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not, however, required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents of the publication without prior permission is always illegal.

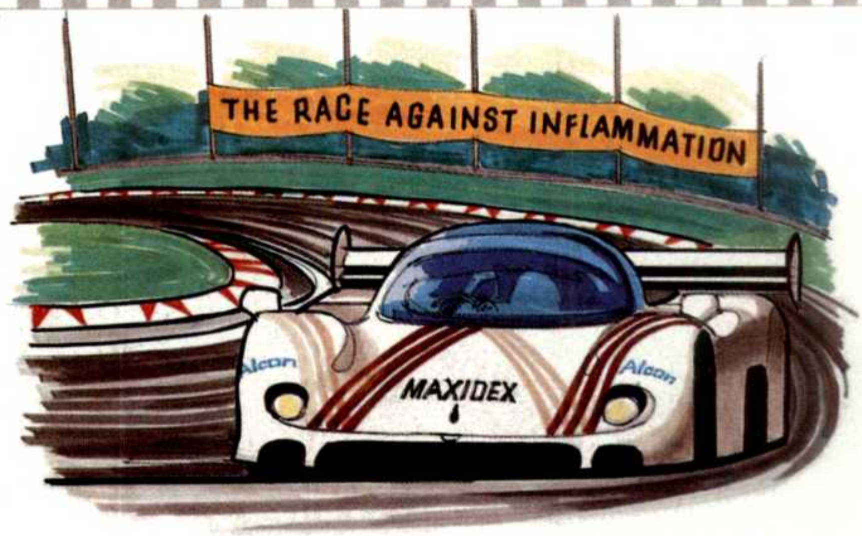
NOTICE TO ADVERTISERS Applications for advertisement space and for rates should be addressed to the Advertisement Manager, *British Journal of Ophthalmology*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *British Journal of Ophthalmology* is published monthly. The annual subscription rates are £106.00 inland and £126.00 overseas (US $200.00). Orders should be sent to the Subscription Manager, British Journal of Ophthalmology, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. All inquiries regarding air mail rates and single copies already published should be addressed to the Publisher in London.

Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd



FAST THROUGH CORNEAS.

MAXIDEX®
Dexamethasone
Ph. Eur. 0.1%
FAST & EFFECTIVE

Maxidex ophthalmic suspension has proven to be a fast and effective treatment for intraocular inflammation.

Fast, because human studies[1] show that levels of dexamethasone were detectable in aqueous humour 20 minutes after topical administration of Maxidex — demonstrating rapid penetration of the human cornea.

Effective, because in the same studies peak levels of dexamethasone were achieved in human aqueous between 91 and 120 minutes after instillation of Maxidex.

Furthermore, 75% of peak concentration is still present after 4 hours, thus maintaining adequate levels between doses.

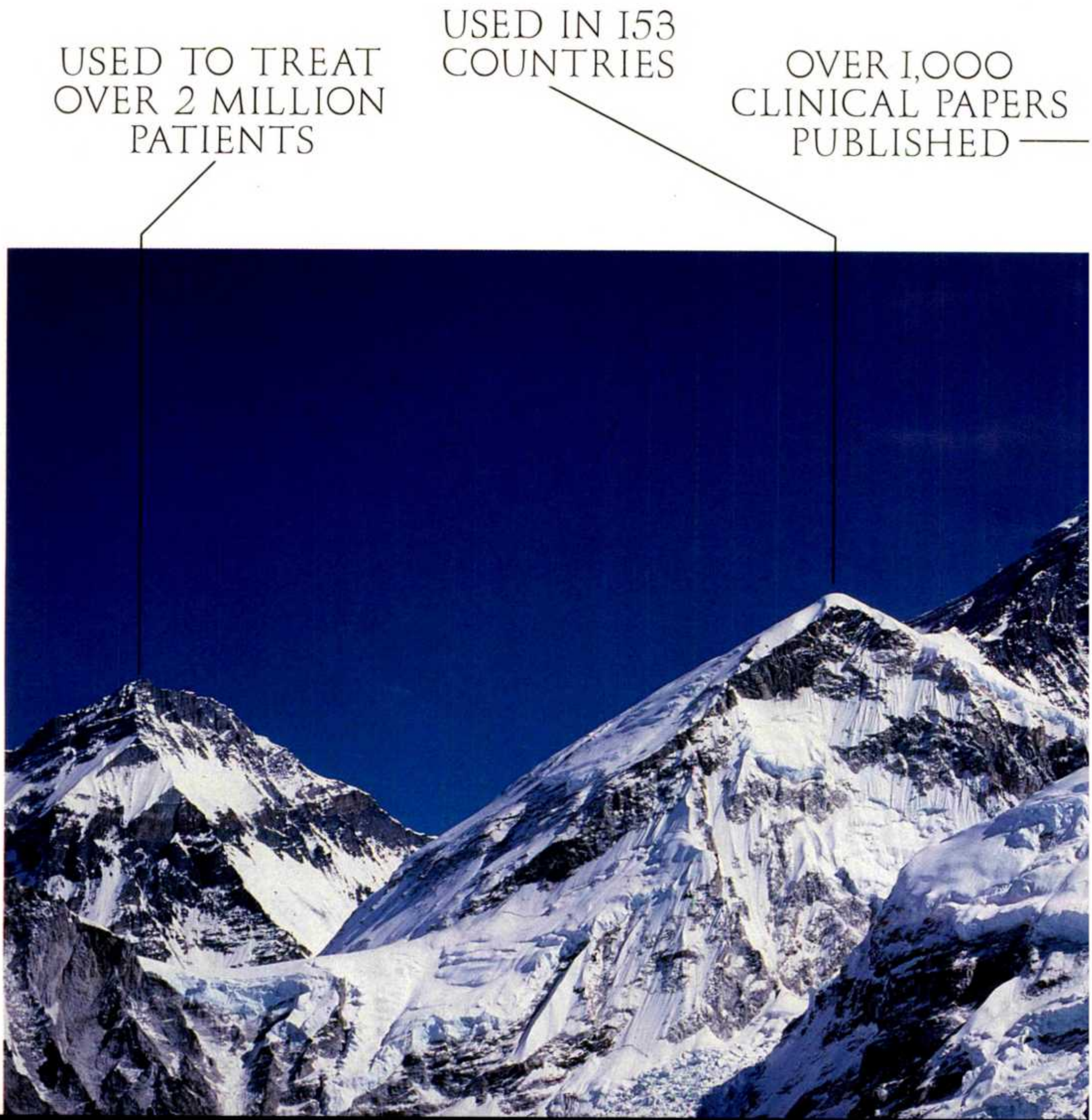
For full information contact Alcon Laboratories.

Alcon
Dedicated to Excellence

Alcon Laboratories (UK) Ltd.,
Imperial Way, Watford, Herts. WD2 4YR
Tel (0923) 246133 Fax (0923) 243331

REFERENCE:1. Watson, D. et al.: Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humor, Arch Ophthalmol 106: 686 687, 1988.

PRODUCT INFORMATION: Presentation: Dexamethasone PhEur 0.1% in a sterile, isotonic, ophthalmic suspension preserved with Benzalkonium Chloride BP 0.01%. **Uses:** Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and administration:** One or two drops topically in the conjunctival sac(s) four to six times daily. In severe disease, drops may be used hourly. **Contra-indications:** Epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; tuberculosis of the eye; and in those persons who have shown hypersensitivity to any component of this preparation. **Warnings:** Use in the treatment of herpes simplex requires great caution. Not effective in the treatment of Sjorgen's keratoconjunctivitis. Infection appears to be enhanced with the presence of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. It is advisable that the intraocular pressure be checked frequently. This product contains benzalkonium chloride and should not be used when soft contact lenses are being worn. **Adverse reactions:** Glaucoma with optic nerve damage, visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe may occur. **Pregnancy warning:** Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long-term treatment of pregnant patients. **Legal category:** POM. **Package quantities:** 5 ml and 10 ml. **P.L.:** 0649/5914.


USED TO TREAT OVER 2 MILLION PATIENTS
USED IN 153 COUNTRIES
OVER 1,000 CLINICAL PAPERS PUBLISHED

WHAT ON EARTH C

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children. *Nursing:* Mother should either stop nursing or stop 'Timoptol'. *Pregnancy:* Not studied; weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, blepha-

12-90 TOT.89 GB.4697.J

Photograph: Mount Everest, Nepal.

USED AS FIRST-LINE
)PEN-ANGLE GLAUCOMA
IERAPY BY THE MAJORITY
F UK OPHTHALMOLOGISTS[1]

OVER 4,600 MILLION
PATIENT DAYS
OF EXPERIENCE

TOP 'TIMOPTOL'?

itis, keratitis, blepharoptosis, and decreased corneal ensitivity. Visual disturbances, including refractory hanges (due sometimes to withdrawal of miotics), iplopia, and ptosis.

radycardia, arrhythmia, hypotension, syncope, eart block, cerebrovascular accident, cerebral chaemia, congestive heart failure, palpitation, ardiac arrest.

ronchospasm (predominantly with pre-existing ronchospastic disease), respiratory failure, dyspnoea.

Ieadache, asthenia, nausea, dizziness, depression.

Iypersensitivity, rash, and urticaria.

eactions with an unestablished relationship are CMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

BASIC NHS COST

0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack. 0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

Product licence numbers:

0.25% Ophthalmic Solution 'Timoptol', 0025/0134.
0.5% Ophthalmic Solution 'Timoptol', 0025/0135.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA. Issued January 1990.

Reference

1. Data on file, Merck Sharp & Dohme Limited.

Ophthalmic Solution
Timoptol®
(timolol maleate, MSD)

JNSURPASSED AS FIRST-LINE GLAUCOMA THERAPY

OH DEAR,
I FORGOT TO TAKE ALL MY DROPS
AGAIN.

What can you give a patient who suffer from amnesia as well as glaucoma?

Getting patients to comply with complicated dose regimens can be a frustrating business.

Which is why Allergan has developed Betagan, the beta blocker most patients only need to take once a day. This is possible because of Betagan's sustained activity over 24 hours,[1] which has been shown to be effective in controlling the intraocular pressure of up to 81% of patients on a once daily dose.[2]

In fact, in a study evaluating once-dail Betagan the authors concluded "once-daily trea ment with levobunolol appeared to be as effectiv as twice-daily treatment while offering greate convenience and comfort and potentially greate safety."[3] So next time you'r looking for a simple but flexibl treatment for open angle gla coma, consider Betagan.

It's a name worth remembering.

NEW

BETAGAN®

(levobunolol hydrochloride 0.5%)

ONCE DAILY

ONE DROP THEY WON'T FORGET

▼ PRESCRIBING INFORMATION

PRESENTATION: Sterile ophthalmic solution containing levobunolol hydrochloride 0.5% (w/v). **ACTION:** Beta-adrenergic blocking agent. **INDICATIONS:** Reduction intraocular pressure in chronic open-angle glaucoma and ocular hypertension. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:** Contraindications: Bronchi asthma; history of bronchial asthma; chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block; cardiac failure; cardiogen shock; hypersensitivity to any component. Caution in labile diabetes and in patients receiving oral beta-adrenergic blocking agents. Do not use in patients continuing to we hydrophilic (soft) contact lenses. Transient ocular burning and stinging on instillation may occur. Bradycardia, hypotension, dyspnoea and asthma have been reported. **DOSAGE:** Adults only: one drop in the affected eye(s) once or twice daily. **PACK SIZE:** 5 ml plastic dropper bottles of 0.5% w/v solution. **BASIC NHS PRICE:** £5.05 PL 0426/0060. Full prescribing information is available on request.

1. Duzman, E. *et al.*, Am J Ophthalmol 1982; *94* (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989: *96* (1): 8-11. 3. Wandel, T. *et al.*, Am J Ophthalmol 1986; *101*: 298-304.

ALLERGAN PHARMACEUTICAL

Allergan Ltd., High Wycombe, Bucks HP12 3S

® Betagan is a registered trade mark.

British Journal of Ophthalmology, 1990, 74, 705

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Photic sneezes

Christmas approaches, and what could be better as a secular text for the festive season than a quotation from *Alice's Adventures in Wonderland*:

> Speak roughly to your little boy,
>   And beat him when he sneezes:
> He only does it to annoy,
>   Because he knows it teases.

Such drastic treatment for one of the minor manifestations of photophobia (although in this case due to pepper) would certainly not be approved by modern paediatricians, for most of whom the old adage of sparing the rod and spoiling the child is at present unfashionable. Nevertheless, the title of the paper in this issue by B Katz and colleagues, 'Photic sneeze reflex in nephropathic cystinosis', provides an irresistible temptation to introduce the quotation.

There is a certain amount in the ophthalmic literature about the biological effects of light, including papers on such curiosities as photophobia in porphyria[1] and astigmatism,[2] the photoconvulsive response,[3] the influence of retinal stimulation on the blood cholesterol,[4] and even the effect of photostimulation on the gonads of the duck.[5] Lewkonia[6] has given an excellent account of the photic sneeze reflex, which is of course familiar to everyone who has ever tried to consummate a promised but tantalisingly suspended sneeze by looking at a bright light.

In the case described by Katz *et al.* in this month's issue cystinosis, in which crystals are deposited in the cornea, was associated in a patient with an enhanced photic sneeze reflex, and one presumes that the mechanism had something to do with the corneal abnormality. The mystery is, how does it work? One had to assume that the close linkage between the eyes and the nose via the trigeminal (Latin: three born at a time, or triplets) nerves must be the mediator, and there is of course another well known linked reflex in this connection, namely, lacrimation on being punched on the nose. There is, however, a slight inconsistency in comparing sneezes and lacrimation, directly linked via the trigeminal nerves, with photic reflexes. The photic reflexes are much harder to explain. Indeed photophobia itself, though obviously valuable as part of a system of protective reflexes, must have a fairly complex pathway in the central nervous system, since it is obvious that light cannot directly stimulate the trigeminal nerve. Nevertheless once photophobia has been initiated it is not difficult to accept a sneeze almost as easily as a blink as a valid part of the process. One can only be grateful to nature that the sneeze factor is usually in abeyance, otherwise we should have to insist on our patients wearing face masks to undergo slit-lamp examination, and one shudders to think what explosions would rock the consulting room during routine indirect ophthalmoscopy.

REDMOND SMITH

1 Berglund H, Kornerup T, Paul KG. The treatment of photophobia in two cases of cutaneous porphyria. *Acta Ophthalmol (Kbh)* 1955; **33**: 247–51.
2 Hellner KA. Photophobia of obscure origin. *Ber Dtsch Ophthalmol Ges* 1967; **68**: 518–9.
3 Procopis PG, Jameson HD. The photoconvulsive response. Modification by monocular occlusion in Man. *Arch Neurol* 1974; **31**: 31–4.
4 Hayashi Y. Studies on the influence of retinal stimulation due to luminous stimuli on the living body. 4. Fluctuations of total cholesterol and ester and the lipoprotein fraction of the blood. *Folia Ophthalmol Jpn* 1970; **21**: 79–95.
5 Benoit J. Photo-neuro-endocrine systems: the role of the eye and hypothalamus in the photo-stimulation of gonads in the duck. *Ann NY Acad Sci* 1964; **117**: 204-16.
6 Lewkonia I. An infrequent response to slit lamp examination. *Br J Ophthalmol* 1969; **53**: 493–5.

British Journal of Ophthalmology, 1990, 74, 706–708

Photic sneeze reflex in nephropathic cystinosis*

Barrett Katz, Ronald B Melles, Michael R Swenson, Jerry A Schneider

Abstract

Photic induced sneeze is a reflex that occurs in certain individuals after exposure to bright light. Cystinosis is an autosomal recessive inborn error of metabolism in which non-protein cystine accumulates within lysosomes. The pathognomonic ocular manifestation of cystinosis is corneal crystal deposition. We observed photic induced sneezes during ophthalmoscopic examination in five of 19 patients with nephropathic cystinosis (26%). We report on this observation and discuss possible pathophysiological mechanisms for photic induced sneezing in cystinosis.

Sneezing in response to bright light is a peculiar phenomenon that may occur in otherwise normal people.[1] It most commonly occurs as a subject walks outside into bright sunlight; on occasion it happens during ophthalmoscopy and rarely with slit-lamp illumination. While numerous investigators have commented on this unique reflex,[2-4] its physiological mechanism has not been clearly defined.

Cystinosis is an autosomal recessive metabolic disorder in which non-protein cystine accumulates in most body organs.[5] The cystine accumulates within the lysosomes of cells owing to a defect in lysosomal cystine transport.[6] Cystinosis is divided into two major clinical groups, nephropathic and benign. Systemic complications of the former include the renal Fanconi syndrome with rickets and growth retardation, and glomerular failure necessitating renal transplantation by an average age of 10 years. All phenotypes of cystinosis are associated with ocular manifestations. The pathognomonic ocular manifestation of cystinosis is the presence of distinctive iridescent crystals within the conjunctiva and cornea. Histologically the crystals are birefringent, intracellular, and of varying morphology.

Crystals have also been seen in the iris, ciliary body, choroid, retinal pigment epithelium, sclera, episclera, extraocular muscles, and optic nerve sheath.[7-9] A pigmentary retinopathy characteristically affecting the periphery has been described in the nephropathic form of the disease,[10] though not observed in the benign form.[11] Although cystine crystals may be deposited in the choroid plexus and on rare occasion are seen within brain parenchyma,[12] patients with cystinosis have been thought to be neurologically normal. Recent work has suggested that these patients do have neurological dysfunction.[13 14] While cystinosis affects many ocular structures, the only complaints of patients are, generally, photophobia and glare.

In the course of our on-going study of the neuro-ophthalmological manifestations of nephropathic cystinosis we observed photic induced sneeze in a disproportionate number of these patients. We report on this observation, and relate its occurrence in cystinosis to a possible underlying pathophysiology.

Patients and methods

We examined 19 patients with the infantile-onset form of nephropathic cystinosis. All had photophobia, though none had excessive lacrimation or obvious nasal allergies. All patients had normal visual acuity with normal colour vision (pseudoisochromatic plates). Their pupillary responses were normal, without evidence of afferent pupillary defect. No sectoral abnormality of iris innervation was noted, and accommodation was normal for age. Corneal reflexes were clinically normal in all the patients, and trigeminal function was intact. On four of the 19 we performed electrophysiological blink reflex studies, with transcutaneous stimulation of the supraorbital nerve and surface recording of the orbicularis oculi motor action potential. In all patients so studied a normal afferent limb to the blink reflex was demonstrated.

All of the cystinosis patients had extensive crystal deposition in the conjunctiva and cornea. Ophthalmoscopy revealed all patients to have depigmentation of the peripheral retina, with a patchy, mottled appearance to each fundus from the mid equator to the ora serrata. Optic nerves were of normal colour, contour, and capillarity. No defect of nerve fibre layer could be detected.

Results

During the course of slit-lamp biomicroscopy two of the 19 patients had a photic induced sneeze, and during indirect ophthalmoscopy three more patients had one. Thus five of 19 (26%) nephropathic cystinosis patients showed this reflex. The sneeze occurred at the beginning of the exposure of the retina to light and did not persist with continued exposure. Pupillary evaluation with a hand held muscle light before slit-lamp examination and indirect opthalmoscopy did not precipitate a photic sneeze in any patient. Of 100 control patients prospectively examined in the same manner none sneezed in

Pacific Presbyterian Medical Center and Smith-Kettlewell Eye Research Institute, San Francisco, CA, USA
B Katz

Department of Ophthalmology, University of California at San Francisco, San Francisco, CA
R B Melles

Department of Neurosciences
M R Swenson

Department of Pediatrics
J A Schneider

University of California at San Diego, La Jolla, CA, USA

Correspondence to:
Barrett Katz, MD, Pacific Presbyterian Medical Center and Smith-Kettlewell Eye Research Institute, 2340 Clay Street, San Francisco, CA 94115, USA.

Accepted for publication 14 June 1990

*Presented in part at the 1988 Neuro-Ophthalmology Congress, 10 May 1988, Vancouver, BC, Canada.

response to the light of the indirect ophthalmoscope or slit-lamp.

Discussion

Collie *et al* characterised the photic induced sneeze as an uncontrollable paroxysm of sneezing provoked in a reflex fashion by the sudden exposure of a dark-adapted subject to intensely bright light.[15] The reported incidence of the photic sneeze reflex is surprisingly high. Peroutka and Peroutka reported it to be present in nine of 25 neurologists (36%), though their data were derived from questionnaires.[16] Everett[1] reported a history of photic sneeze in 68 of 414 persons (16·4%) surveyed. He found a higher incidence in Caucasians than blacks, and in those who had noted the reflex in family members, and he concluded that heredity was a factor in predisposing to photic sneeze. In a study of four families Collie *et al* found a distribution consistent with an autosomal dominant inheritance pattern for the trait, with a high degree of penetrance.[15]

The usual source of stimulation in susceptible people is sunlight, though artificial light may also precipitate a sneeze. Sedan described the reflex in patients exposed to such varying stimuli as the indirect ophthalmoscope, photographic flash, and ultraviolet light.[17] Although generally harmless, photic induced sneezing has been reported to cause conduction deafness, mediastinorrhexis, and cerebral haemorrhage.[15] Moreover, the photic sneeze reflex may be more than just a curiosity to those whose work requires exposure to flashes of illumination.[15]

Sedan[17] and Everett[1] noted a feature seen also in the current study, namely that the sneezing occurred at the beginning of the exposure of the retina to bright light but did not persist with continued exposure or when the exposure was soon repeated. The stimulating light seems to precipitate the reflex when it follows a period of relative darkness. Elicitation of the reflex produces a latency interval during which the retina is refractory to further photic induced sneezing.

What does the prevalence of photic sneeze in cystinotic patients say about the underlying pathophysiology of this reflex? Our patients with nephropathic cystinosis all had corneal infiltration with cystine crystals. The occurrence of this reflex in the setting of corneal dysfunction has been recognised previously,[3] and keratitis has been reported to enhance the photic sneeze reflex.[17 18] Lewkonia described a man with corneal oedema and vascularisation following alkali burn.[3] The patient sneezed during ophthalmoscopic and slit-lamp examination. He was seen daily for his keratopathy, and the progression of his photic sneeze was recorded. The occurrence of sneeze reflex decreased as the cornea healed. Keratopathy, however, is neither a necessary nor sufficient criterion for photic sneeze.

Another hypothesis for photic induced sneeze reflex invokes optic-trigeminal summation.[1] Eckhardt *et al* postulated that stimulation of the optic nerve enhances the irritability of the trigeminal nerve.[19] Photic stimuli may produce referred sensation in fibres carried by the first division of the trigeminal nerve.[19] Such summation may involve the second division of the trigeminal, thus enhancing nasal stimulation to the point of precipitating the sneeze synkinesis.[1] Wirtschafter and Bourassa concluded that trigeminal nerve stimulation may greatly increase sensitivity to light.[20] Such interactions could explain the photophobia observed in patients with cystinosis.

The cystinotic patient may have an underlying irritability of the trigeminal nerve related to crystal deposition in the cornea. The peripheral branches of the trigeminal nerve behave abnormally in cystinosis.[21] This is postulated to be secondary to altered function in the basal epithelial neural plexus and penetrating anterior corneal nerves or their end organs, corresponding to the recognised site of maximal cystine crystal deposition.[21 22] Peripheral trigeminal dysfunction may incite an alteration in more central control mechanisms, culminating in trigeminal supersensitivity and susceptibility to ephaptic transmission. The trigeminal nerve may become especially sensitive to both stimulus generalisation and stimulus summation. Watson stated that the photic sneeze 'occurs most frequently when there is a morbid sensitiveness [of] . . . the fifth [nerve] . . . centrally reflected to the retina.'[18] Light falling on the retina stimulates afferent fibres to the pretectal nuclei, which then send interneurons to the Edinger-Westphal nuclei. The parasympathetic fibres from the Edinger-Westphal nuclei and the trigeminal afferent fibres from the cornea both pass through the ciliary ganglion, where they may participate in ephaptic transmission.

Parasympathetic generalisation may contribute to photic sneeze. Stimuli which excite primarily one branch of the parasympathetic nervous system tend to activate other branches.[1] Light falling on the retina stimulates pupillary contraction, subserved by parasympathetic fibres of the oculomotor nerve. The parasympathetic activity of miosis may produce congestion of and secretion from the nasal mucosa (mediated through the seventh nerve and the sphenopalatine ganglion), factors which are recognised to initiate sneezing.[23]

In summary, the photic induced sneeze is a reflex which seems to involve diverse neuroanatomical substrates including the optic, oculomotor, and trigeminal nerves, autonomic pathways, and central brainstem structures. Its remarkable prevalence in a nephropathic cystinosis population offers an opportunity for further study of its underlying pathophysiological mechanisms.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness (BK).

1 Everett HC. Sneezing in response to light. *Neurology* 1964; 14: 483–90.
2 Kofman O. Paroxysmal sneezing. *Can Med Assoc J* 1964; 91: 154–7.
3 Lewkonia I. An infrequent response to slit lamp examination. *Br J Ophthalmol* 1969; 53: 493–5.
4 Everett HC. Reply to Pratt AG. Photic sneezing [Letter]. *JAMA* 1965; **191**: 153–4.
5 Schneider JA, Schulman JD. Cystinosis. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease.* New York: McGraw-Hill, 1983: 1844–66.
6 Jonas AJ, Smith MD, Schneider JA. ATP-dependent lysosomal cystine efflux is defective in cystinosis. *J Biol Chem* 1982; 257: 13185–8.

7 François J, Hanssens M, Coppieters R, Evens L. Cystinosis: a clinical and histopathologic study. *Am J Ophthalmol* 1972; **73:** 643–50.

8 Sanderson PO, Kuwabara T, Stark W, Wong VG, Collins EM. Cystinosis: a clinical, histopathologic and ultrastructural study. *Arch Ophthalmol* 1974; **91:** 270–4.

9 Frazier PD, Wong VG. Cystinosis: histologic and crystallographic examination of crystals in eye tissues. *Arch Ophthalmol* 1968; **80:** 87–91.

10 Wong VG, Lietman PS, Seegmiller JE. Alterations of pigment epithelium in cystinosis. *Arch Ophthalmol* 1967; **77:** 361–9.

11 Lietman PS, Frazier PD, Wong VG, Shotton D, Seegmiller JE. Adult cystinosis – a benign disorder. *Am J Med* 1966; **40:** 511–7.

12 Ross DL, Strife CF, Towbin R, Bove KE. Nonabsorptive hydrocephalus associated with nephropathic cystinosis. *Neurology* 1982; **32:** 1330–4.

13 Trauner DA, Chase CH, Scheller JM, Katz B, Schneider JA. Neurologic and cognitive deficits in children with cystinosis. *J Pediatr* 1988; **112:** 912–4.

14 Katz B, Melles RB, Trauner DA, Schneider JA. Saccadic abnormalities in nephropathic cystinosis. *J Clin Neuro Ophthalmol* 1988; **8:** 115–9.

15 Collie WR, Pagon RA, Hall JG, Shokeir MHK. ACHOO syndrome (Autosomal Dominant Compelling Helio-Ophthalmic Outburst syndrome). *Birth Defects* 1978; **14:** 361–3.

16 Peroutka SJ, Peroutka LA. Autosomal dominant transmission of the 'photic sneeze reflex.' *N Engl J Med* 1984; **310:** 599–600.

17 Sedan J. Reflexe photo-sternutatoire [photo-sternuatatory reflex]. *Rev Oto-neuro-ophtal* 1954; **26:** 123–6.

18 Watson WS. *Diseases of the nose and its accessory cavities.* London: Lewis, 1875: 343.

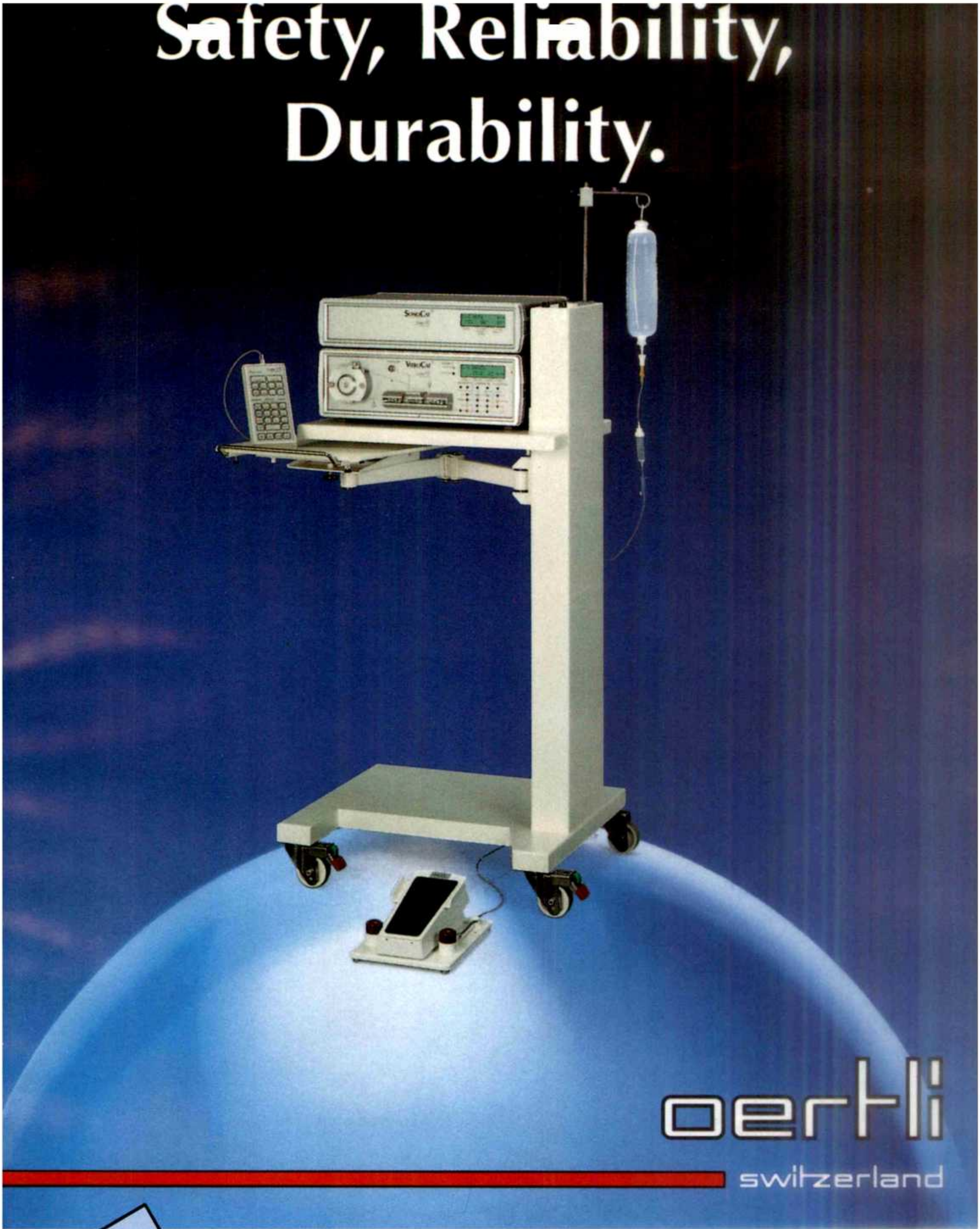
19 Eckhardt LB, McLean JM, Goodell H. The genesis of pain from the eye. *Assoc Res Nerv Mental Dis Proc* 1943; **23:** 209–7.

20 Wirtschafter JD, Bourassa CM. Binocular facilitation of discomfort with high luminances. *Arch Ophthalmol* 1966; **75:** 683–8.

21 Katz B, Melles RB, Schneider JA. Corneal sensitivity in nephropathic cystinosis. *Am J Ophthalmol* 1987; **104:** 413–6.

22 Melles RB, Schneider JA, Rao NA, Katz B. Nephropathic cystinosis: spatial and temporal sequence of corneal crystal deposition. *Invest Ophthalmol Vis Sci* 1987; **28** (suppl): 222.

23 Brubaker AP. The physiology of sneezing. *JAMA* 1919; **73:** 585–7.



VITROCAT
tion/aspiration system

SONOCAT
phaco emulsification system

Sole Agents in the U.K.

Clement Clarke International Ltd
Airmed House, Edinburgh Way, Harlow, Essex CM20 2ED
Tel 0279 414969 Tlx 81338 Fax 0279 635232

RESCRIBING INFORMATION

PRESENTATION

clear colourless solution in a plastic dropper bottle. lauline is available in two strengths containing 0.1% 0.3% w/v metipranolol together with benzalkonium loride 0.01% w/v as a preservative.

USES

lauline is a beta adrenoceptor blocking agent used in e topical treatment of chronic open-angle glaucoma d other conditions in which intra-ocular pressure is evated above normal levels.

DOSAGE AND ADMINISTRATION

dults and the elderly: The recommended dosage is one op instilled into the affected eye(s) twice daily.

hildren: Not Recomended.

ewly diagnosed patients with ocular hypertension or ronic open-angle glaucoma should be treated with lauline 0.1%, changing to the higher strength if lequate control of intra-ocular pressure is not achieved maintained. Patients on existing therapy, whether or ot this is to be continued, should receive Glauline 0.3%.

CONTRAINDICATIONS, WARNINGS, ETC

ontraindications: Bronchial asthma, history of onchial asthma, chronic obstructive airways disease, nus bradycardia, second or third degree rio-ventricular block, cardiac failure, cardiogenic ock, hypersensitivity to any of the components of the eparation.

ecautions and Warnings: As with other topically plied beta-blockers, systemic absorption may occur ving adverse reactions similar to those of orally lministered beta-blockers. Cardiac and respiratory actions have been reported with topically applied eta-blockers including, rarely, death due to onchospasm or cardiac failure. Congestive cardiac ilure should be adequately controlled before starting erapy with Glauline. If the patient has a history of rdiac disease, pulse rate should be monitored. iabetic control should be monitored during Glauline erapy in patients with labile diabetes. There have been ports of granulomatous anterior uveitis occuring in tients using Glauline. In any case, where a patient ows symptoms or signs suggestive of anterior uveitis, lauline should be withdrawn and an alternative ocular potensive agent substituted. Glauline contains nzalkonium chloride as a preservative and should erefore not be used in patients continuing to wear soft ydrophilic) contact lenses. Use in pregnancy: lthough there is no evidence to suggest that etipranolol has teratogenic properties, its use during egnancy should be avoided unless the potential nefits are considered to outweigh the possible hazards.

se in lactation: As beta-blockers can pass into breast ilk, consideration should be given to stopping east-feeding if therapy with Glauline is considered cessary.

de-effects:

Ocular: Transient burning or stinging on instillation, urred vision, superficial punctate keratitis, epharoconjunctivitis and anterior uveitis have been ported.

Cardiovascular: Bradycardia and hypotension can casionally occur following the systemic absorption of pically applied beta-blockers.

Respiratory: Bronchospasm can occur, edominantly in patients with a history of reversible structive airways disease. Dyspnoea and respiratory ilure have also been reported with topically applied ta-blockers.

CNS: Headache, ataxia, weakness and lethargy can cur.

Dermatological: Local manifestations of contact nsitivity reactions around the eyes can involve skin shes on the lower lids and cheeks, and peri-orbital dema.

ug interactions: Caution should be exercised if used conjunction with oral beta-blockers as additive effects systemic beta blockade may occur. Overdosage: verdosage is unlikely by the ocular route. If excess ug is accidentally administered to the eye, the affected e(s) should be immediately flushed with water or line. If accidental or deliberate systemic ingestion has ken place, bronchospasm, bradycardia, hypotension d cardiac failure may result, and treatment for erdosage of a beta-receptor blocking agent should be itiated.

PHARMACEUTICAL PRECAUTIONS

auline should not be diluted or dispensed from any ntainer other than the original bottle. The unopened oduct has a shelf life of 3 years, but as with other eye ops the contents of each bottle should be discarded one onth after opening.

LEGAL CATEGORY POM

PACKAGE QUANTITIES

auline is supplied as a sterile ophthalmic solution in a nl plastic dropper bottle.

FURTHER INFORMATION

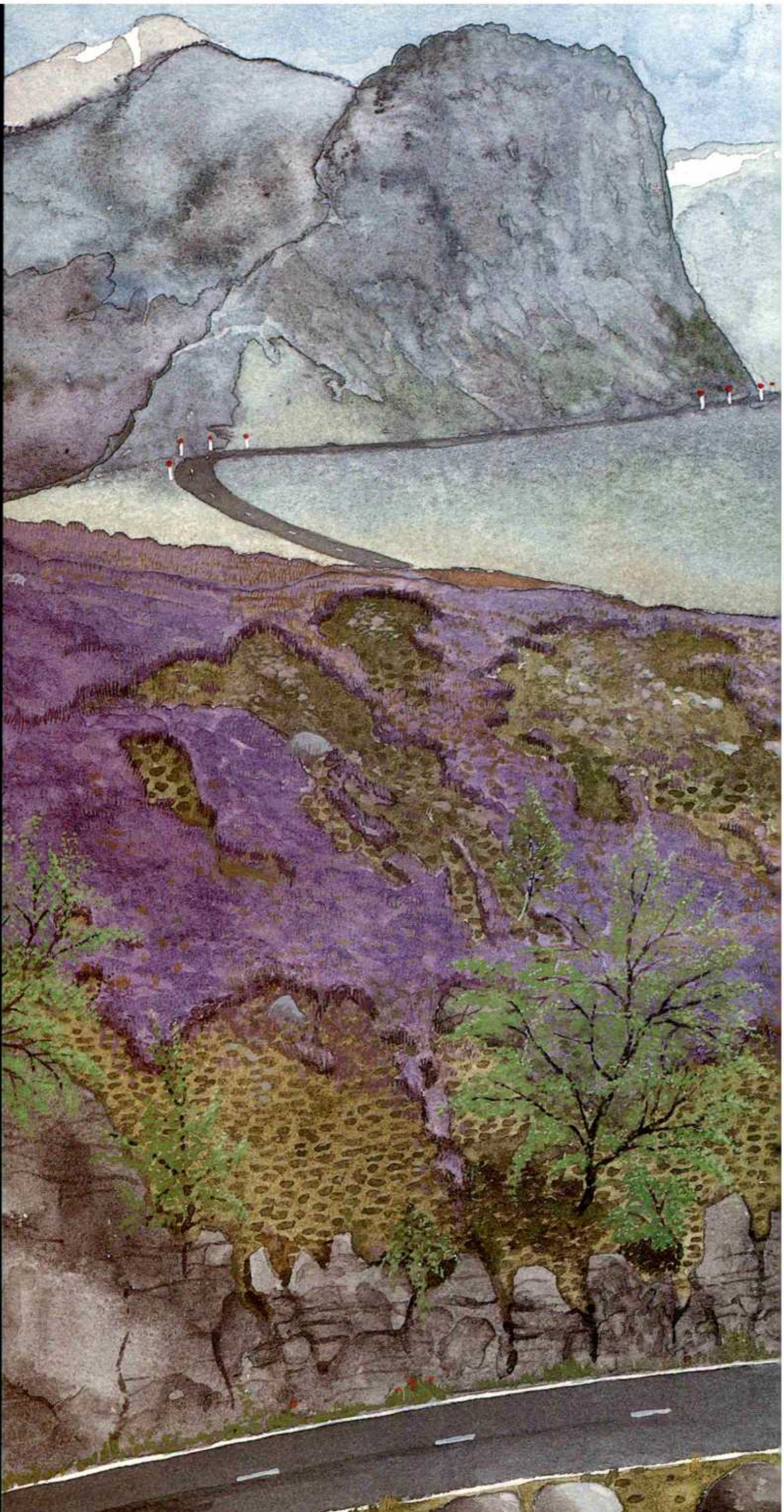
auline reduces intra-ocular pressure with little or no fect on pupil size or accommodation. For newly agnosed glaucoma patients, clinical trial experience ggests that approximately 85% will achieve adequate ntrol of their intra-ocular pressure with Glauline 0.1%.

PRODUCT LICENCE NUMBERS

auline 0.1% 0033/0104
auline 0.3% 0033/0105

BASIC NHS PRICE

nl - 0.1% £4.03, 0.3% £4.67.



Glauline*

METIPRANOLOL

*Trade Mark

Take the low road

Smith & Nephew Pharmaceuticals L

Bampton Road, Harold Hill,
Romford, Essex RM3 8SL, England
Telephone: Ingrebourne (04023) 49
Telex: 898 058 SMINEPG
Fax: 04023 71316

Fucithalmic
fusidic acid
Contains Fucidin fusidic acid
twice daily for bacterial conjunctivitis

▼ Prescribing Information.

Presentation: Sterile viscous drops of a 1% aqueous sustained release formulation of fusidic acid preserved with benzalkonium chloride. **Uses:** Fucithalmic is active against Staphylococcus aureus, Streptococcus, Neisseria, Haemophilus, Moraxella and Corynebacteria. The sustained release formulation of Fucithalmic ensures a prolonged contact with the conjunctival sac. Twice daily application provides sufficient concentrations in all relevant tissues of the eye. Fucithalmic penetrates well into the aqueous humour. **Indications:** Bacterial conjunctivitis due to sensitive organisms. **Dosage:** One drop to be instilled into the eye twice daily. Treatment should be continued for at least two days after the eye returns to normal. **Contra-indications:** Hypersensitivity to any component. **Precautions:** Should not be used when contact lenses are being worn. **Side effects:** Transient stinging. Hypersensitivity may occur. **Product Licence Number:** 0043/0137. **Basic N.H.S. Price:** £2.25/5g tube.

LEO

Further information available on request:
Leo Laboratories Limited
Longwick Road, Princes Risborough
Aylesbury, Bucks HP17 9RR

British Journal of Ophthalmology, 1990, 74, 709–711

When is it safe to stop patching?

John G Oster, John W Simon, Paul Jenkins

Abstract

Prior reports indicate that about half of amblyopia patients successfully treated with occlusion subsequently require maintenance patching. This retrospective study was designed to discover what clinical characteristics might be associated with a stable outcome following primary occlusion. Included were 188 patients who: (1) had amblyopia related to strabismus, anisometropia or media opacity; and (2) were followed up for at least one year after successful primary occlusion. Patients who did not comply with treatment or who did not achieve equal vision were excluded. Their ages ranged from 2 to 119 months (mean 29 months). Eighty-eight patients (47%) who required no further occlusion were designated the clinically stable group (CSG). The remaining 100 (53%), who subsequently needed patching because of unequal acuities, constituted the maintenance patching group (MPG). CSG patients were older at the beginning (mean 33 months) and at the end (mean 40 months) of primary occlusion than were MPG patients (means 26 and 31 months). Primary occlusion was more likely to have been discontinued because of equal recognition acuities in CSG patients, while equal fixation behaviour or preferential looking was more likely in MPG patients. Distribution of diagnoses, severity of amblyopia at presentation, and length of follow-up were similar in the two groups. Visual outcomes at last follow-up were slightly better in the CSG (p=0·002). We conclude that, in general, patching can be safely discontinued after the third birthday. Although follow-up after primary occlusion is important to ensure stable results in all patients, preverbal children are more likely to require maintenance patching.

It is generally recognised that intensive occlusion can achieve normal or nearly normal visual acuity in most amblyopic eyes, especially when treatment is begun early in childhood.[1-4] Prior reports indicate that 40–52% of children who are successfully treated with primary occlusion will subsequently require maintenance patching.[2 5] Some of these patients may suffer an actual recurrence of amblyopia, while others previously considered cured may be discovered to have unequal vision when more sensitive testing becomes possible with advancing age. In either case intensive occlusion is typically reinstituted until the best possible acuity is achieved. Part-time maintenance occlusion may then be required, often for long periods during childhood.

Although the long-term prognosis in amblyopia and the proportion of patients requiring maintenance occlusion have been reported in several series,[2 5 6] the characteristics associated with the need for maintenance occlusion have rarely been studied.[2] This retrospective study compares two groups of patients successfully treated with primary occlusion: the first group achieved a stable outcome following primary occlusion and the second group required maintenance occlusion. Comparisons focus on differences noted before and during treatment which might demonstrate when primary occlusion can safely be concluded.

Department of Ophthalmology, Albany Medical College, Albany, New York, USA
J G Oster
J W Simon
P Jenkins

Correspondence to
John W Simon, MD,
Department of
Ophthalmology, Pinnacle
Place, McKown Road,
Albany, New York 12203,
USA.

Accepted for publication
7 June 1990

Patients and methods

The records were reviewed of 403 consecutive patients treated with occlusion for amblyopia by JWS between 1981 and 1988. The children ranged in age from 1·9 to 119·1 months (mean 29·4 months) at the beginning of occlusion. All had manifest strabismus in the primary position, unilateral or asymmetric media opacities, or anisometropia of at least 1·0 D spherical equivalent or cylinder power. Children who were noncompliant or unresponsive to treatment were excluded, as were children followed up for less than one year after primary occlusion was completed. Also excluded were children with nystagmus, macular or optic nerve lesions, congenital glaucoma, severe neurological impairment, and occlusion amblyopia. A total of 188 patients were thus identified for further study.

The presence or absence of amblyopia was determined, at the outset of treatment and at subsequent follow-up intervals, according to a uniform procedure. In literate patients projected Snellen letters were used, and amblyopia was diagnosed if corrected acuities differed by two lines or more between eyes. In preliterate verbal patients projected Allen pictures were used and amblyopia was diagnosed if corrected acuities differed by one line or more. In preverbal patients with strabismus amblyopia was inferred if there was a fixation preference, unless preferential looking indicated equal acuities. In preverbal patients without strabismus or with strabismus and indeterminate fixation amblyopia was inferred if their preferential looking was unequal, if there was an objection to a cover over the other eye, or if following or reaching was more accurate with the other eye.

Nearly full-time occlusion was initially prescribed for all patients, with recommended follow-up intervals of one week per year of age. Spectacle or contact lens correction of ametropia or anisometropia was prescribed where indicated in addition to occlusion. For all patients primary occlusion was continued as long and as intensively as needed, until amblyopia was no longer demonstable by the above clinical tests. Patients were then followed up without occlusion.

Of the 188 patients 88 (47%) had a stable outcome following primary occlusion and are designated the clinically stable group (CSG). In this group equal or nearly equal acuities were consistently demonstrated without the need for further patching. We compared this group with the 100 patients in whom unequal acuities were subsequently demonstrated, the maintenance patching group (MPG). Patching was reinstituted in this group an average of 7·6 months (SD 8·3 months) following primary occlusion and was continued an average of 29·6 months (SD 18·6 months). MPG patients were patched intensively until maximum improvement in the amblyopic eye was again demonstrated. Part-time occlusion was then instituted as necessary to maintain the recorded improvement. Follow-up intervals were decreased from one week per year of age proportionate to the patching intensity (for example, two weeks per year for half-time patching).

Characteristics reviewed included: reason for initiating primary occlusion, diagnosis (strabismus, anisometropia, media opacity, or strabismus plus anisometropia), visual acuity and refraction when primary occlusion began, the age treatment began, duration of primary occlusion, the age primary occlusion discontinued, the reason treatment discontinued, length of follow-up after primary occlusion discontinued, the reason occlusion reinstituted, duration of maintenance occlusion, and visual acuity at last follow-up.

Results

There was no significant difference between the CSG and MPG in diagnoses (Table 1) or in reason for initiating primary occlusion (Table 2). Table 3 lists other characteristics likewise found not to be significantly different between groups: duration of primary occlusion, length of follow-up, anisometropia, and (for verbal patients) visual acuity or severity of amblyopia.

Primary occlusion was begun for the CSG at age 33·2 (SD 21·7) months and for the MPG at 26·2 (SD 21·4) months. This age difference was significant (p=0·028). Patching was initially discontinued at 40·0 (SD 22·6) months for the CSG and at 31·3 (SD 22·9) months for the MPG. This age difference was also significant (p=0·009). Fig 1 shows a linear relationship between the age at which primary occlusion was stopped and the proportion of patients with a stable outcome. Fig 2 shows the distribution of ages at which primary occlusion was stopped. The reason for discontinuing occlusion in the two groups were significantly different (p=0·01), as shown in Table 4. Those patients whose recognition acuities were tested were more likely to be in the CSG (48/84, 57%) than those whose fixation or PL acuities were assessed (40/104, 38%). The reasons for starting maintenance occlusion in the MPG are listed in Table 5.

A total of 77 MPG patients were followed up at least 12 months after maintenance patching was begun. Interocular differences in visual acuity at last follow-up in this group were compared with those of the CSG. A small but statistically significant difference (p=0·003) was apparent: 0·12 (SD 0·21) octave for the CSG versus 0·28 (SD 0·42) octave for the MPG.

Table 1 Diagnosis

	CSG	*MPG*
Media opacity	3	3
Anisometropia	6	9
Strabismus	63	68
Strabismus and anisometropia	16	20

Table 2 Reason for initiating primary occlusion

	CSG	*MPG*
Not alternating or maintaining fixation	69	83
Unequal Allen picture acuities	14	13
Unequal Snellen acuities	5	4

Table 3 Characteristics not related to stable outcome

	CSG (mean (SD))	*MPG (mean (SD))*
Duration of primary occlusion	6 9 (9·1)	5·1 (7·7)
Length of follow-up	34·0 (18·7)	37·2 (18·4)
Anisometropia (spherical equiv)	+0·85 (2·5D)	+0·92 (1 9D)
(cylinder power)	+0·39 (0 51D)	+0·58 (0·95D)
Visual acuity (verbal patients, in octaves)	0·80 (0·33)	1·11 (0·83)

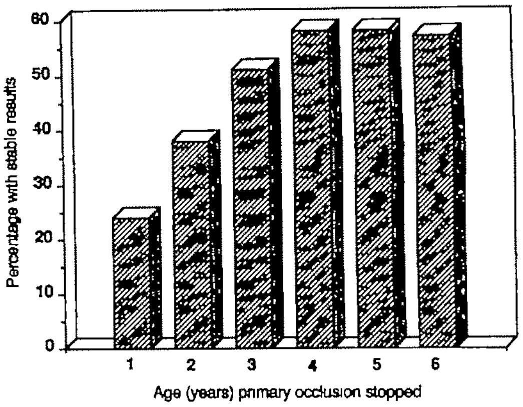


Figure 1 Relation between age at which occlusion was stopped and clinical stability.

Discussion

Ching, Parks, and Friendly investigated 116 strabismic amblyopia patients, among whom 52% required maintenance patching after primary occlusion had been terminated.[2] The 53% incidence of maintenance patching in our series is almost identical. However, the prior study

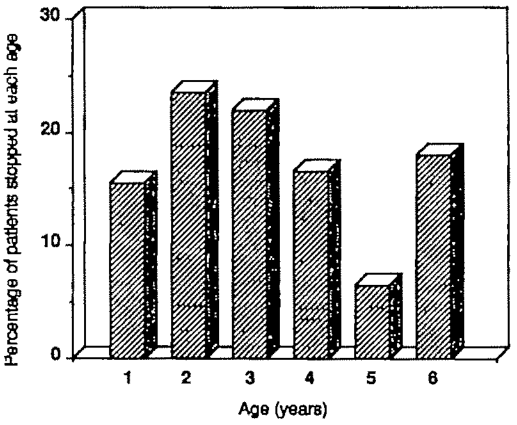


Figure 2 Distribution of ages when primary occlusion was stopped.

Table 4 Reasons for concluding primary occlusion

	CSG	*MPG*
Equal Snellen acuities	8	7
Equal Allen acuities	40	29
Alternation or well maintained fixation in each eye	31	55
Equal preferential looking acuities	9	9

Table 5 Reasons for starting maintenance occlusion

Unequal Snellen acuities	13
Unequal Allen picture acuities	25
Unequal fixation	55
Unequal preferential looking acuities	7

found the only significant difference between groups to be more severe amblyopia among maintenance patching patients at the outset of therapy. In our study verbal CSG and MPG patients had similar levels of amblyopia. Because of uncertainty in quantifying visual acuity using fixation behaviour we chose not to mix preverbal and verbal patients in determining mean visual acuities. MPG patients had more severe amblyopia at last follow-up. This difference was clinically small but statistically significant.

Our experience suggests that age was an important factor in predicting stability following primary occlusion. CSG patients were significantly older than their MPG counterparts at the beginning and at the end of primary occlusion. This relationship between stability and age at the end of primary occlusion was strong, particularly during the first four years (Fig 1). The association between stability and recognition acuity, as opposed to preferential looking or fixation acuity, probably reflects the same relationship: only older patients are verbal and thus able to participate in recognition acuity assessment.

Jastrzebski *et al*[7] devised a model of amblyopia which describes its response to occlusion. 'Sensitivity' indicates a propensity for the patched eye to worsen and for the amblyopic eye to improve. All patients in our series were sensitive, as indicated by improvement in the amblyopic eye. The model then distinguishes, among the sensitive eyes, some which are 'elastic' from others which are 'plastic'. Elasticity implies reversibility, after occlusion is discontinued, of improvement in the amblyopic eye, and of damage in the patched eye. Plasticity implies a permanent change in both eyes. While others have associated younger age with greater sensitivity,[3] our study suggests that younger age may be associated with greater elasticity as well. Interestingly, Jastrzebski and associates also found loss of elasticity with advancing age during the childhood years.

In this context maturation of the visual system can be seen as rendering permanent the improvement in amblyopic vision effected by patching. Our data indicate that this stability becomes evident between the third and fourth birthdays. Follow-up after primary occlusion is important to ensure stable results in all patients. Younger children, however, are more likely to require maintenance patching than older patients and should be followed closely, even when patching seems unnecessary.

This work was supported in part by Training Grant EYO7O37O2 and Research Grant EYO5816 from the National Institutes of Health, National Eye Institute, and by an unrestricted grant from Research to Prevent Blindness to the Albany Medical College Department of Ophthalmology

1 Noorden GK von. *Binocular vision and ocular motility*. 2nd ed St Louis: Mosby, 1980: 431–9
2 Ching FC, Parks MM, Friendly DS Practical management of amblyopia. *J Pediatr Ophthalmol Strabismus* 1986; 23: 12–6
3 Greenwald MJ, Parks MM. Treatment of amblyopia In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Lippincott, 1988; 1: chapter 11.
4 Fulton AB, Mayer DL. Esotropic children with amblyopia: effects of patching on acuity *Graefes Arch Clin Exp Ophthalmol* 1988; 226: 309–12.
5 Scott WE, Dickey CF. Stability of visual acuity in amblyopic patients after visual maturity *Graefes Arch Clin Exp Ophthalmol* 1988; 226: 154–7.
6 Sparrow JC, Flynn JT. Amblyopia. a long-term follow-up. *J Pediatr Ophthalmol Strabismus* 1979; 14: 333–6.
7 Jastrzebski GB, Hoyt CS, Marg E. Stimulus deprivation amblyopia in children. Sensitivity, plasticity, and elasticity (SPE). *Arch Ophthalmol* 1984; 102: 1030–4

British Journal of Ophthalmology, 1990, 74, 712–716

Peripheral contrast sensitivity in glaucoma and ocular hypertension

Fernando Falcão-Reis, Eamonn O'Donoghue, Rosaria Buceti, Roger A Hitchings,
Geoffrey B Arden

Department of Clinical Ophthalmology, Institute of Ophthalmology and Electrodiagnostic Clinic, Moorfields Eye Hospital, London EC1
E O'Donoghue
R A Hitchings
G B Arden

Department of Ophthalmology, Oporto Medical School, Oporto, Portugal
F Falcão-Reis

Institute of Ophthalmology, Policlinico Universitario de Messina, Gazzi, Italy
R Buceti

Correspondence to:
Professor G B Arden,
Electrodiagnostic Clinic,
Moorfields Eye Hospital, City Road, London EC1V 2PD.

Accepted for publication
14 June 1990

Abstract

Contrast sensitivity has been measured in patients with glaucoma and ocular hypertension, the latter graded into high, medium, and low risk clinical groups. Measurements were made centrally and peripherally at 10°, 15°, 20°, and 25° off-axis at each of the four meridians 45°, 135°, 225°, and 315°. A sine wave grating of 1·9 cycles/degree, reversing at 1 Hz was used. It was displayed on a 100-Hz refresh rate monitor. Normal values were established to compare those from 41 eyes from patients with either primary open angle glaucoma (POAG) with minimal field loss detectable on a Humphrey perimeter, or raised IOP and/or disc changes but no field loss (OH). Those with POAG had normal central contrast sensitivity, but at 20° and 25° eccentricity the values were >2 standard deviations above the normal mean. This was also the case for high risk OH, but not for low risk patients. All the high risk patients except one who had abnormal peripheral contrast sensitivity had possible field defects (threshold elevation at one or more points more than 5 but less than 10 dB above normal mean). Only one of those with normal peripheral contrast sensitivity had such 'suspect points'. The results are assessed in terms of screening of glucoma suspects.

Primary open angle glaucoma (POAG) is diagnosed when a patient has demonstrable visual field defect and either a raised intraocular pressure (IOP) or clinical signs, such as disc changes, which are consistent with a raised IOP, and no other complicating causes for the raised pressure. There are several tests which aid diagnosis. Perimetric loss defines the condition,[1] but its sensitivity is not great enough to detect the earliest pathological changes: 40% of optic nerve axons are lost before any visual defect is apparent.[2] Increases in pressure occur long before field is lost, and the degree of increase in IOP gives an indication of the probability that the patient will subsequently develop a characteristic field loss.[3] However, it is impossible to screen for glaucoma on the basis of ocular pressure measurement only. No level of IOP can be found at which the percentage of 'false positives' *and* 'false negatives' is acceptable.[4] Examination of the optic nerve head, especially with stereoscopic viewing, is an efficient and effective method of detecting damage to the optic nerve, but it requires expert judgment.[5] A further limitation derives from the fact that patients who do not have any pathological process may have discs which seem abnormal.[6]

Another problem in treating glaucoma is to decide when to begin. It is often considered to be too late to wait until a frank field defect is found[7-9] and so one should treat patients with raised IOP and/or disc changes but no field loss (OH) in whom the condition is progressing. Estimates from the measurement of IOP are of limited use in deciding when to treat, as is a slight increase in a high cup/disc ratio. Therefore various subclassifications of OH have been devised in an attempt to quantify the risk that field loss may develop, and only patients in high risk groups are treated.[10] This limits the cost of treatment and minimises the possibility of adverse reactions. To a considerable extent risk classification rests on clinical judgment. Recently some other diagnostic methods have been used to detect and grade the small degree of damage to the optic nerve which occurs in OH – for example, colour discrimination measured with desaturated colours[11] or colour contrast sensitivity.[12] The pattern electroretinogram[13] especially has been found abnormal in ocular hypertension and appears to be more successful than the psychophysical techniques in detecting abnormality in glaucoma and high risk OH, possibly because a large retinal region is tested, while psychophysical methods measure only macular or even foveal function.

Another method claimed to detect visual changes in glaucoma and OH is the measurement of contrast sensitivity. Several techniques have been used,[14-17] and testing is as fast, easy to perform, and inexpensive as is required for screening. Unfortunately, early hopes of sensitivity and specificity of that method were not realised.[18] Although losses in contrast sensitivity at low spatial frequency occur in patients suffering from glaucoma and OH, there is an unacceptable overlap with normals, even when the grating pattern is modulated as a function of time (which improves detection of early losses[19]). Another unexploited value of temporally modulated gratings is that with them the Troxler effect is absent, and it is thus possible to measure contrast sensitivity in untrained subjects as far peripherally as 25–30° from the fovea. There have been no previous reports of such measurements in OH patients, but since the first field loss occurs peripherally it seems likely that the first losses of contrast sensitivity will occur in such regions. We have accordingly measured peripheral contrast sensitivity in eyes with early glaucoma and ocular hypertension at different risks of conversion of glaucoma. By the time glaucomatous eyes show the earliest evidence of visual field defect, that is, one spot of 10 dB loss, contrast sensitivity is greatly reduced when measured in the periphery. Determination of contrast sensitivity in four quadrants at 20° or 25° (four points) served to separate all eyes with glaucoma from normal eyes, while testing at the macula was totally ineffective. Furthermore, in 50% of eyes with high risk ocular hypertension there are definite losses of contrast sensitivity at an eccentricity of 20° and 25°.

Material and methods

A TV monitor controlled by a T221 grating generator (Faulkner-West Associates) was used to present a vertical sinusoidal grating in a pattern reversing mode. The refresh rate was 100 Hz. Thus there was no 'TV flicker' even for peripheral viewing. Contrasts as low as 0·1% could be generated. The TV screen was surrounded by a white card of 80×80 cm, on which small fixation spots were affixed at appropriate locations. Most of the TV screen was also covered by the card except for an 8 cm round area in the middle. In this hole 6 cycles of the grating could be seen. Patients sat in a chair at 1·2 m from the screen. At this distance stimulus and surround subtended 3·8° and 33° respectively. Spatial frequency was 1·9 cycles/degree. An abrupt reversal (square wave) with a temporal frequency of 1 Hz was used. Both remained unchanged during testing. The mean luminance of the TV screen was 80 cd/m^2. Daily calibrations of contrast and luminance were carried out with a Tektronix J16 photometer. Room illumination was 10 cd/m^2. The operator sat at the side of the monitor, facing the patient, to check fixation. Threshold was determined by the method of ascending limits. Contrast, defined in the usual manner, was increased slowly and smoothly by the manual operation of a 10-turn calibrated potentiometer either from zero or from a variable subthreshold value. Patients were instructed to respond as soon as they could detect motion of the pattern. At least three measurements were averaged to determine a threshold at each locus. In a few cases the stimulus lay on a scotomatous region of retina, so no meaningful measurement could be made. In such cases the threshold contrast was arbitrarily given a value of 30%. Pupil diameter was not measured, but none of the patients was treated with miotics.

Patients and subjects wore spectacles when appropriate. Tests were carried out monocularly. The grating had an unchangeable spatial frequency, so no pattern preview was given. No time limit was imposed. Contrast threshold were measured at 10°, 15°, 20°, and 25° eccentricity at the 45°, 135°, 225°, and 315° meridians: these were chosen so that the blind spot was avoided. In addition the threshold was measured with foveal viewing. A full examination – 17 loci each eye – took about 45 minutes. All contrast sensitivity determinations were carried out by the same operator, who was not aware of the patients' condition.

Forty-one eyes (mean age of patients 57 (SD 8) years, 27% female, 73% male) with glaucoma or hypertension recruited from a glaucoma clinic and 11 eyes (mean age of subjects 49 (SD 12) years, 36% female, 64% male) with normal eyes were examined. Hospital staff members with no ocular or systemic diseases volunteered as controls.

The doctors who carried out the contrast sensitivity test did not recruit the patients and did not carry out any clinical examinations, and were not aware of the field test results.

The patients' eyes were examined by biomicroscopy, fundoscopy, disc photography, applanation tonometry, and Humphrey computerised static perimetry, and were classified by the usual criteria as suffering from either glaucoma or ocular hypertension (Table 1). Glaucomatous eyes had a reproducible visual field defect defined as one or more spots of sensitivity loss of 10 dB or greater at least in two different occasions plus one adjacent spot of 5 dB. Hypertensive eyes were further classified into three groups.[20] The low risk group had an intraocular pressure below 26 mmHg and a vertical cup to disc (C/D) ratio less than 0·6. Eyes with either an intraocular pressure equal to or greater than 26 mmHg or a C/D ratio equal to or greater than 0·6 were classified as medium risk. The high risk group included eyes with intraocular pressure greater than 26 mmHg and C/D ratio greater than 0·6. Additionally eyes with OH were classified as 'suspects' when loci in the sites tested by the Humphrey 30-2 program had a sensitivity loss greater than 5 dB but less than 10 dB.

Exclusions. Patients and normal subjects had a visual acuity of 6/6 or better and no ocular disease particularly cataract or corneal opacities. None had systemic hypertension, diabetes, or other disease.

Results

CENTRAL RETINAL CONTRAST SENSITIVITY

Each patient or observer was asked to look directly at the grating, and contrast sensitivity was measured. The mean value of the macular region in normal control eyes was 0·91% (SD 0·13). This was not significantly less than the contrast sensitivity of low and medium risk OH groups.

The difference between the normals and the high risk group was greater, though the significance was only $0{\cdot}1>p>0{\cdot}05$. Glaucomatous eyes showed a significant loss of sensitivity ($p>0{\cdot}001$). Of greater interest is the distribution of contrast sensitivity in the population. This is shown in Fig 1. For central viewing, in two out of eight cases of glaucoma the thresholds were just below the upper limit of normal. This sort of overlap has previously been reported and explains why central contrast sensitivity (CS) is not an adequate screening technique.

Table 1 Classification criteria

	Normal	*Low risk*	*Medium risk*	*High risk*	*Glaucoma*
IOP (mmHg)	<21	≥21, <26	≥26	≥26	Any
		and	or	and	
C/D ratio	<0·6	<0·6	≥0·6	≥0·6	≥0·6
Visual field	Normal	Normal or suspect	Normal or suspect	Normal or suspect	Abnormal

Suspect: one or more spots ≥5 dB ≤ 10 dB.
Abnormal: one or more spots ≥10 dB plus 1 spot ≥5 dB.

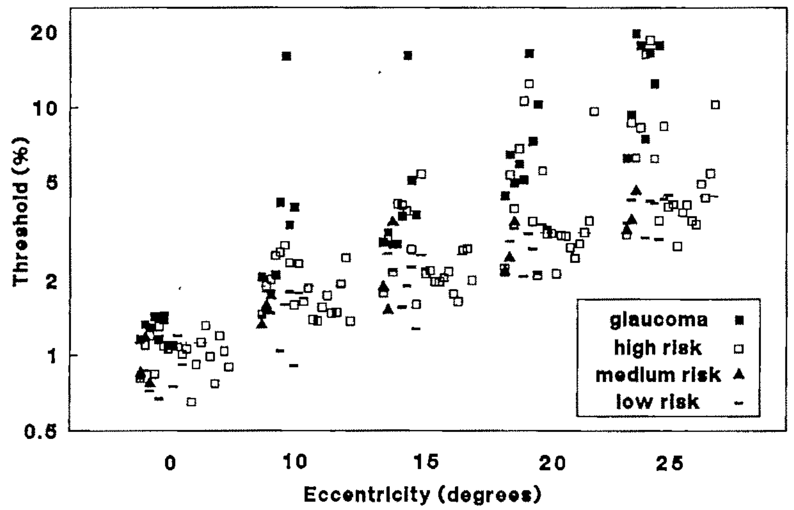


Figure 1 Distribution of mean contrast sensitivity as a function of retinal eccentricity. All individual results shown. Each symbol represents (except for central viewing) the average of results from four loci, one in each quadrant. The different symbols refer to the patients' diagnoses. The dotted line represents the upper limit of normal (mean+2 SD). It can be seen that contrast sensitivity decreases from the centre to the periphery. Note that two glaucomatous eyes give results within the 5% confidence limit for foveal testing. However, for peripheral viewing the distinction between the results in glaucoma and the upper limit of normal is much more evident. For patients with high risk OH the proportion with reduced contrast sensitivity also increases from centre to periphery and reaches 50% at 25°.

Table 2 Mean contrast sensitivity of four quadrants

	Category of patient				
Retinal position	*Normal*	*Low risk OH*	*Medium risk OH*	*High risk OH*	*Glaucoma*
Central					
Mean	0·91	0·93	0·93	1 03	1·25
SD	0·13	0·23	0·22	0·17	0·14
Significance*		NS	NS	<0·1	<0·001
10°					
Mean	1·57	1·51	1·54	1·89	4·34
SD	0·20	0·33	0·21	0·46	4·78
Significance*		NS	NS	<0·05	<0·05
15°					
Mean	2·01	2·03	2·27	2·59	5·00
SD	0·30	0·43	1·01	1·0	4 54
Significance*		NS	NS	<0·1	<0·05
20°					
Mean	2·56	2·76	2·69	4·50	7·58
SD	0·31	0·54	0·66	3 00	4·00
Significance*		NS	NS	<0·05	<0·001
25°					
Mean	3·63	3·90	3·76	6 47	13 30
SD	0·47	0 62	0 74	4·30	5·19
Significance*		NS	NS	<0·05	<0 001

**t* Test of normal against each class of patient. figure is probability that the result could be obtained by chance NS=not significant.

PERIPHERAL CONTRAST SENSITIVITY

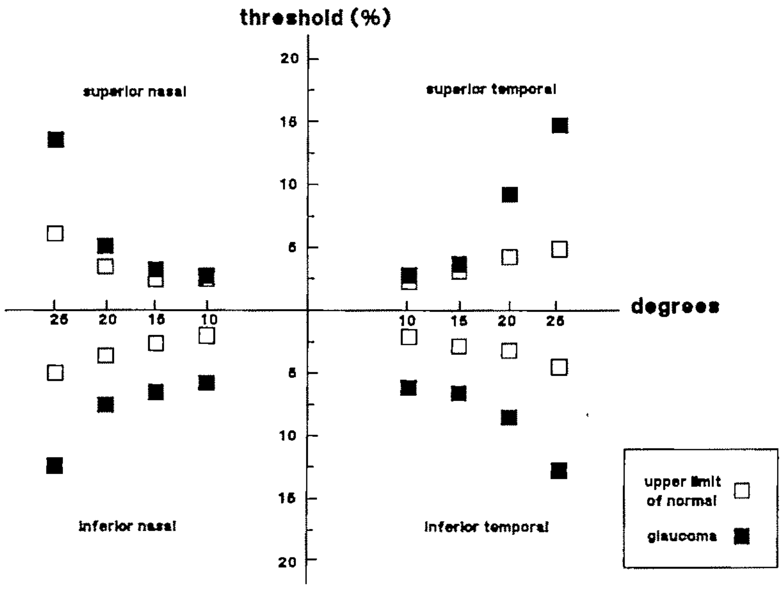
Normals

Mean values for measurements in all four quadrants and the SD are shown in Table 2. Contrast sensitivity at most eccentric positions was considerably less than with central fixation, and decreased with eccentricity. The upper limits of normal (mean+2 SD) are represented by the horizontal dotted lines on the graph of Fig 1. These results are consistent with previous findings.[15 18 19]

Glaucoma

The distribution of individual results is shown for peripheral CS in Fig 1. Fig 2 shows the average contrast thresholds at each retinal position. Note that for normals the symbols are at the mean plus 2 SD. In the superior quadrants of the visual field the difference between glaucomatous eyes and controls at 10° and 15° is small, but in the lower quadrants it is quite evident. In the two most peripheral loci (20° and 25°) the difference between the two groups is clear in all quadrants. For glaucomatous patients, contrast sensitivity, averaged over the four quadrants (Fig 5) is significantly lower than for the normals (the p values range from <0·005 to <0·001 depending on eccentricity). Note that the difference between normal and glaucomatous eyes is less in the superior nasal quadrant, where the scotomata are less frequent.

Figure 2 Contrast sensitivity at eccentric loci in glaucomatous eyes. Results are compared with upper limit of normal (mean+2 SD). Each symbol represents the mean of thresholds of all glaucomatous eyes at a given locus. Difference between normals and glaucomatous eyes is evident at all loci in the lower field and at 20° and 25° in the superior quadrants. Loss of sensitivity in glaucomatous eyes is less pronounced in the superior nasal quadrant.



Not only are the differences between means significant, but the discrimination between affected and normal is nearly complete if the results from each of the four quadrants are averaged as in Fig 1.

There is only one false negative at 10° and none at 15°, 20°, and 25°. It might be considered that this averaging biased the result, since contrast sensitivity would be zero over a scotoma. Contrast sensitivity is not directly related to luminance incremental threshold (which is measured by perimetry, but evidently when increment threshold is infinity (that is, the stimulus lies on an absolute scotoma) the contrast threshold must also be immeasurably high. Only five eyes had a threshold higher than 30%. Among these one glaucomatous eye had a threshold higher than 30% at four retinal loci in one quadrant. These were scored as 30% (see 'Methods' section). Thus the results given in the figures under-represent the difference between normal and glaucomatous eyes.

OCULAR HYPERTENSION

Low risk group

Some differences between normal persons and OH patients can be observed. Low risk OH eyes had an average contrast sensitivity that was consistently *less* than the upper limit of normal (Fig 3) at all retinal eccentricities. When the results of all quadrants were averaged, the results

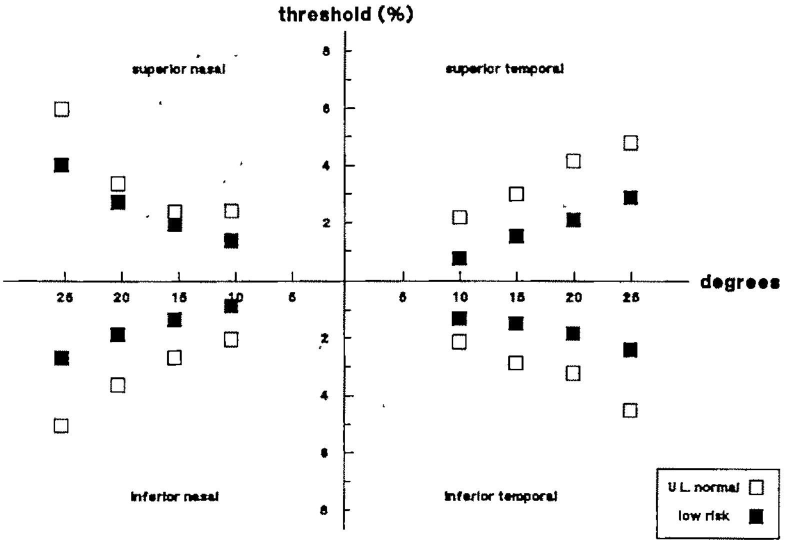


Figure 3 Contrast sensitivity at eccentric loci in low risk hypertensive eyes. Results are compared with upper limit of normal (mean+2 SD). Each symbol represents the mean of thresholds of all eyes at a given locus. Thresholds are similar in all quadrants. Mean contrast sensitivity is consistently under the upper limit of normal.

were also under the upper limit of normal for all eccentricities (Fig 5). As might be expected, the differences between this group and normal controls were not statistically significant (Table 2). Fig 1 shows the individual results, averaged over four quadrants, for the low risk group: only in two individuals, at 20°, were the results above the upper limit of the normal mean. Even in some low risk patients there was evidence of retinal damage, and a proportion of patients progressed to frank glaucoma. The few high thresholds encountered may indicate such lesions, but to provide evidence for this would require prolonged follow-up. More important, the finding that most low risk patients have results within our normal range shows that there is a low incidence of false positives.

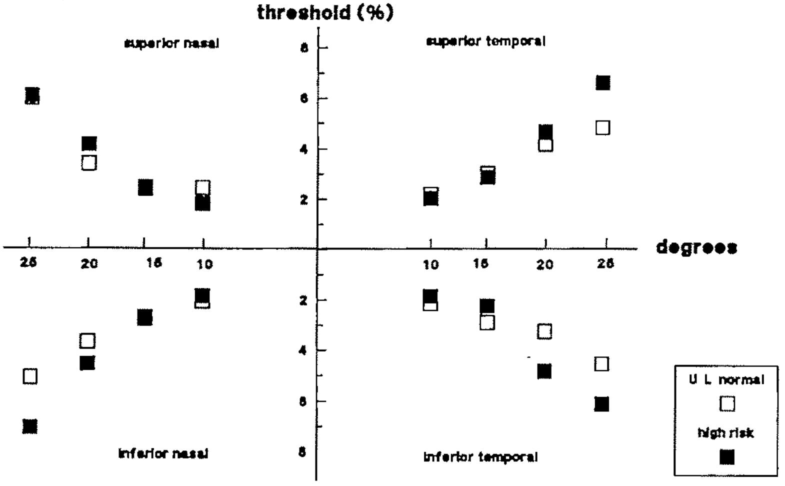
Medium risk group

The medium risk group included only three eyes and results for each quadrant are not shown. Fig 5 shows the mean contrast sensitivity of all quadrants, and it can be seen that is within normal limits.

High risk group

Fig 4 shows the mean results obtained in each locus in the four quadrants. These are compared with the upper limit of normal from the normal population. For 10° and 15° off fixation the two sets of symbols overlap, but for 20° and 25° in seven of the eight determinations the OH eyes' thresholds were significantly raised.

Figure 4 Contrast sensitivity at eccentric loci in the eyes of patients with high risk OH. Results are compared with the upper limit of normal (mean+2 SD). Each symbol represents the mean of thresholds of all eyes at a given locus. There is overlap between the upper limit of normal and high risk OH eyes. Again, loss of sensitivity is less accentuated in the superior nasal quadrant. Note the different scale of ordinate compared with Figure 2.



The exception was the upper nasal quadrant at 25°. Therefore the results for all four quadrants were averaged, as shown in Fig 5. Loss of sensitivity in the two most peripheral positions is very evident in Fig 5, and this difference between high risk OH and normals is significant (0·005>p>0·001). Abnormal thresholds at 25° and 20° were found in 50% and 40% respectively of high risk eyes (30% and 24% of total OH eyes). If individual results are considered, at 25° of eccentricity the group of high risk eyes and a single medium risk eye had abnormal thresholds. Among the high risk cases which were abnormal were eyes in which there was a 'doubtful' field defect, defined as a determination in which threshold was raised at one or more spots by more than 5 dB but less than 10 dB. 50% of high risk eyes had thresholds under the upper limit of normal. Table 3 shows that there was a nearly complete separation of the two groups. The presence of possible field defects was associated with reduced contrast sensitivity, and in those patients who had normal contrast sensitivity 'possible' field defects were infrequent. It should be emphasised that this finding was made only after the end of the project, when the codes were broken. The Fisher exact probability that the two factors are unrelated is vanishingly small, p=0·0000238.

Discussion

In this study simple techniques were used to measure contrast sensitivity in patients' peripheral retina. Such measurements can be made reliably in our population, which, however, is selected: the patients know they are in several clinical trials and are highly motivated. Likewise our normal values are not obtained from spouses, and are not strictly age matched. However, this is not of importance for this project, in which the relation between peripheral and central contrast sensitivity (in the same individuals) is to be compared. Problems related to general screening are discussed below.

We have shown that, by comparison with normal people, patients with glaucoma have raised contrast thresholds for gratings of low spatial frequency, but this is true only for peripheral retina. (It would be difficult to investigate high spatial frequencies in the retinal periphery.) Abnormal peripheral contrast sensitivity in glaucoma has already been reported.[21 22] In addition we have investigated patients with OH, and in some of these too contrast thresholds are raised. In patients with no definite field defects, but with clinical signs which suggest that retinal damage is occurring, there seems to be a highly significant loss of peripheral contrast sensitivity. This might be expected, for it is known that in experimental glaucoma those neurons responsible for the detection of low spatial frequencies and of movement, which subserve the magnocellular system, are selectively affected early in the course of disease.[23]

Furthermore, the present results show normal

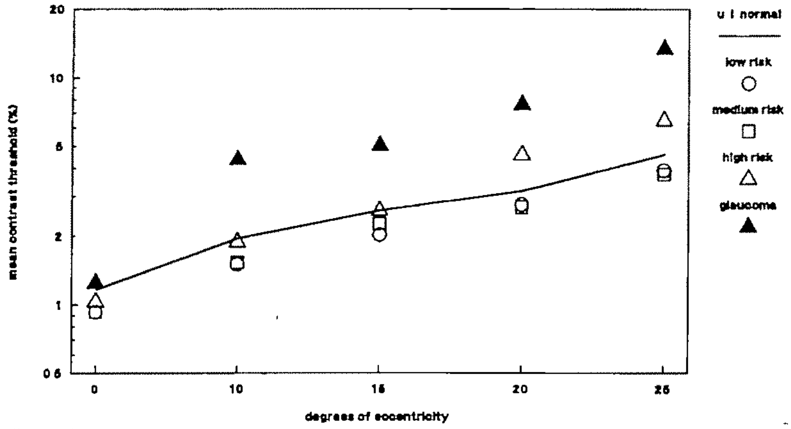


Figure 5 Mean contrast sensitivity averaged over all four quadrants. The symbols refer to different categories of patient, as indicated. The figure shows how the average of contrast sensitivity at four quadrants changes with eccentricity. The line represents upper limit of normal (mean+2 SD). It can be seen that the thresholds of high risk OH eyes are above normal but only at eccentricities of 20° and 25°. The eyes of patients with field loss have thresholds that are just above normal at the fovea but become greatly elevated at all other loci. Low risk and medium risk OH eyes have thresholds that are under normal limits both at the centre and at all peripheral loci.

contrast sensitivity in the retinal periphery of patients with low and medium risk OH. In these patients there is only a low probability that field loss will later develop. Thus it is plausible that the 50% of cases of high risk OH eyes with abnormalities represent that subpopulation which will progress to frank field loss. If so, this would represent a significant improvement in deciding the prognosis of all suspects.

These findings once more raise the possibility that contrast sensitivity might be useful for glaucoma screening. Our results cannot be extrapolated to the entire age group at risk, in which contrast sensitivity losses occur for a variety of reasons.

One way of improving the discrimination would be to test separately in the central and peripheral retina. It should be noted that for central losses our results are less impressive than, for example, Atkin *et al* found.[19] This suggests that our estimate of the upper limit of normal was if anything too high, and the discrimination attainable between normals and OH and glaucoma in the peripheral retina is the more interesting. Thus it is likely that measurements in the retinal periphery might reliably detect (and quantify) retinal damage which precedes field loss.

In order to make screening practicable, our technique requires modification. The prime need is to increase the speed of the test and to use forced-choice methods to minimise the subjective elements. In addition it appears that tritan colour vision losses are more prominent than luminance losses,[12] and this is the case especially for the retinal periphery.[24] Once modifications in technique along such lines have been tested, an alternative to prolonged field testing seems possible.

Table 3 Analysis of results in 20 patients with high risk OH

	*Abnormal CS**	*Normal CS*
Normal visual field	1	10
Suspect visual field	8	1
Total	9	11

*Contract sensitivity. Values of CS are the mean of four quadrants at 25° Fisher exact, p=0·0000238.

Falcao-Reis acknowledges the assistance of the Calouste Gulbenkian Foundation, Lisbon.

This work was supported by grants from Wellcare Trust, Moorfields locally organised research fund, and from the Woolfson Trust (GBA).

1 Becker-Schaffer S. *Diagnosis and therapy of the glaucomas* 6th ed St Louis: Mosby, 1989. 163.
2 Quigley JA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. *Arch Ophthalmol* 1982; 100: 135–46.
3 Anderson DR. Glaucoma. the damage caused by pressure XLVI Edward Jackson memorial lecture. *Am J Ophthalmol* 1989; 108: 485–91
4 Mundor T, Zimmerman TJ, Nardim GF, Kendall KS Automated perimetry, tonometry and questionnaire in glaucoma screening. *Am J Ophthalmol* 1989; 108: 505–8.
5 Drance SM. Correlation of optic nerve and visual field defect in simple glaucoma. *Trans Ophthalmol Soc UK* 1975; 95: 288–96.
6 Bengtsson B. The variation and covariation of cup and disk diameters. *Acta Ophthalmol (Kbh)* 1976; 54: 801–18
7 Epstein DL, Krug JH, Hertzmark E, Remis L, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989, 96: 1460–7.
8 Becker B, Morton WR. Topical epinephrine in glaucoma suspects *Am J Ophthalmol* 1966; 62: 272–7.
9 Jay JL, Donald A. The benefit of early trabeculectomy versus conventional management in primary open angle glaucoma relative to severity of disease. *Eye* 1989; 3: 528–35.
10 Trick Gl, Bickler-Bluth M, Cooper DG, Kolker AE, Nesher R. Pattern reversal electroretinograms (PRERG) abnormalities in ocular hypertension. correlation with glaucoma risk factors. *Curr Eye Res* 1988; 7: 201–6.
11 Airaksinen PJ, Lakowski R, Drance SM, Price M. Color vision and retinal nerve fiber layer in early glaucoma. *Am J Ophthalmol* 1986; 101: 208–13.
12 Gunduz K, Arden GB, Perry S, Weinstein G, Hitchings R Color vision defects in ocular hypertension and glaucoma Quantification with a computer driven color television system. *Arch Ophthalmol* 1988; 108: 929–35.
13 Arden GB, Jacobson J. A simple grating test for contrast sensitivity: preliminary results indicate value for screening glaucoma. *Invest Ophthalmol Vis Sci* 1978; 17: 23–32.
14 Vaegan, Halliday BL. A forced choice test improves clinical contrast sensitivity testing. *Br J Ophthalmol* 1982; 66: 477–91.
15 Regan D, Neima D. Low contrast letter charts as a test of visual function. *Ophthalmology* 1983; 90: 1192–220.
16 Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci* 1988; 2: 187–99.
17 Arden GB. Testing contrast sensitivity in clinical practice. *Clin Vis Sci* 1988; 2: 213–24.
18 Atkin A, Bodis-Wollner I, Wolkstein M, Moss A, Podos SM Abnormalities of central contrast sensitivity in glaucoma. *Am J Ophthalmol* 1979; 88: 205–11
19 Yablonski M, Zimmerman T, Kass M, Becker B. Prognostic significance of optic disk cupping in ocular hypertensive patients. *Am J Ophthalmol* 1980; 89: 585–92.
20 Korth M, Horn F, Storck B,. Jonas J. Spatial and spatiotemporal contrast sensitivity of normal and glaucoma eyes *Graefes Arch Clin Exp Ophthalmol* 1989; 277: 428–35.
21 Lundh BL, Lennerstrand G. Eccentric contrast sensitivity loss in glaucoma *Acta Ophthalmol (Kbh)* 1981; 59: 21–4
22 Quigley HA, Dunkelberg GR, Green WR. Retinal cell atrophy related with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 1989; 107: 453–64.
23 Hart WM Jr, Silverman SE, Trick G, Nesher R, Gordon MO. Glaucomatous visual field damage. *Invest Ophthalmol Vis Sci* 1990; 31: 359–67.

For those patients who should avoid taking nonselective ocular beta blockers...

“Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group.”[1]

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

A bright outlook for glaucoma patients

For effective control of IOP minimising the risks associated with nonselective beta-blockade[2,3,4]

TWICE DAILY

Betoptic®

OPHTHALMIC SOLUTION BETAXOLOL HCl

The only ß$_1$ selective ocular beta blocker

SELECTIVE β_1 BETA-BLOCKADE

PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS AND PRECAUTIONS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic has demonstrated a low potential for systemic effects, it should be used with caution in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. Although cardioselective beta-blockers have less effect on lung function than non-selective beta-blockers caution should be exercised in the treatment of glaucoma patients with obstructive pulmonary disease. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have been reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depressive neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies have not demonstrated any specific hazard there are no adequate and well-contr studies in pregnant women. Because animal studies are not always predictive of human response this c should be used during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is known whether Betoptic is excreted in human milk, caution should therefore be exercised when Beta is administered to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic be flushed from the eye(s) with warm tap water. **BASIC NHS PRICE** £5.30 per 5ml dropta **PRODUCT LICENCE HOLDER AND NUMBER:** Alcon Laboratories U.K. 0649/0097.

DATE OF PREPARATION: SEPTEMBER 1

REFERENCES: 1. Jones FL. Ekberg NL. Letter N Eng J Med 1979; **301**: 270.
2. Levy NS. Boone L. Ellis E. Glaucoma 1985; **7**: 54-62.
3. Schoene RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984;**97**: 86-92.
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

Further information is available on request

Alcon

SPECIALISTS IN EYE CARE
Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR
Telephone (0923) 246133 Fax (0923) 243331
® denotes registered trademark of Alcon Laboratories

British Journal of Ophthalmology, 1990, 74, 717–722

Precapsular film on the aging human lens: precursor of pseudoexfoliation?

Anthony J Dark, Barbara W Streeten

Abstract

In many older patients we observed a layer of subtle opacification on the anterior lens capsule, appearing as a ground glass film biomicroscopically. This precapsular film (PCF) could be uniform but often had radial grey lines in the mid zone, holes in the paracentral region, and was occasionally rolled up in strings. Lens capsular material obtained at cataract extraction was studied in patients with and without the film. By scanning electron microscopy the PCF appeared as a friable, incomplete fibrillar layer, with rolling of the edges suggesting loose attachment. Ultrastructurally its component fibrils were from 3–6 nm in diameter, similar to the finer fibrils in pseudoexfoliation (PSX) material. Like PSX material the layer stained positively for the elastic microfibril-associated protein, fibrillin, in a lens with radial striations. These similarities suggested that the two conditions have some relationship and that the PCF may be a precursor of PSX. Finding patches of the fibrillar network in some control patients imples that the PCF is common in patients of cataract age, though seldom detected clinically.

Department of Ophthalmology, State University of New York **Health Science Center at Syracuse, Syracuse, New York 13210, USA**
A J Dark

Department of Pathology
B W Streeten

Correspondence to:
Dr B W Streeten, Department of Pathology, Weiskotten Hall, SUNY Health Science Center, 766 Irving Avenue, Syracuse, New York 13210, USA.

Accepted for publication
21 June 1990

Most authors tacitly assume that the classical bull's eye or sunburst appearance of frosting on the anterior lens capsule in pseudoexfoliation (PSX) appears suddenly, fully developed, and thereafter undergoes little change (Fig 1). The early biomicroscopic changes are not well recognised and have seldom been reported.[1,2] It is difficult to account for this deficit except to speculate that these changes may be of such transience and subtlety that they are seldom observed and variously interpreted. Bartholomew[1] considered that grey striae on the mid zone of the anterior lens capsule were the earliest biomicroscopic change, the 'pregranular' stage, followed by deposition of vegetations or granules (Busacca's nodules). Evidence for this hypothesis included unilateral cases of PSX associated with striae in the contralateral eye, sector deposition of granules on the striae in some eyes, and a decreasing frequency of striae with age, coinciding with an increase in the granular or established phase.

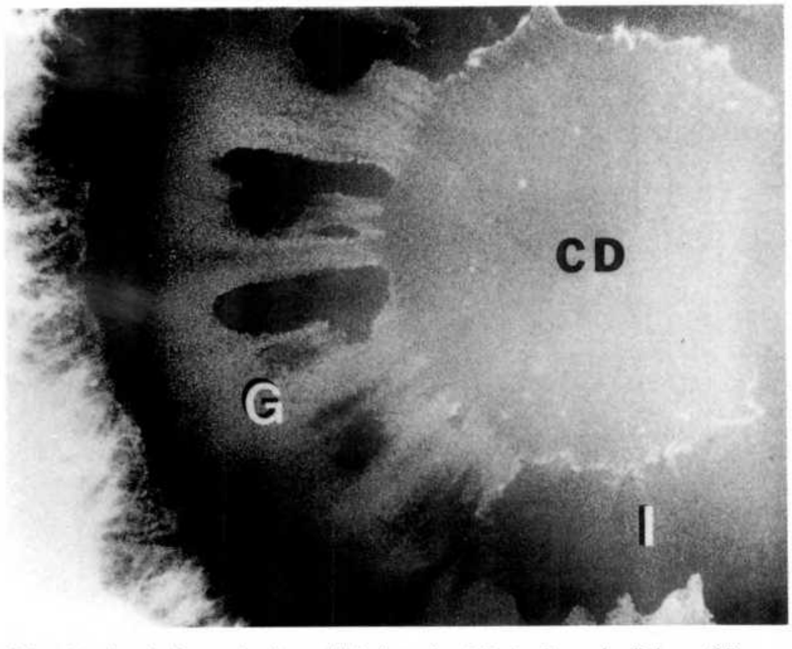


Figure 1 Anterior lens surface in established pseudoexfoliative disease by slit lamp. CD= central disc, G=granular vegetative zone, I=intermediate zone.

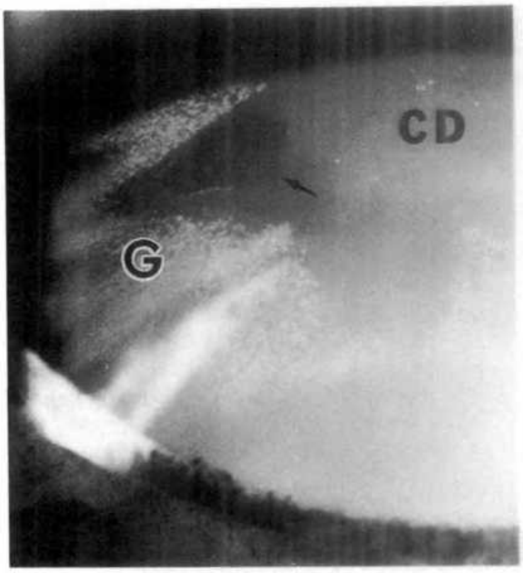


Figure 2 Anterior lens in pseudoexfoliative disease showing white granular zone (G) lying on a homogenous surface film with a paracentral erosion (arrow). CD=central disc.

In a slit-lamp study of patients with and without PSX observed over several years we have noted that the PSX vegetations in some appeared to be deposited on a diffuse but mildly opacified surface layer which sometimes showed focal erosions (Fig 2). A small group of patients in the same age range but without PSX vegetations had a similar ground-glass film on the anterior lens surface, along with other characteristics leading us to hypothesise that the film might be the earliest stage of PSX, before the deposition of granules. This precapsular film (PCF) was a very subtle opacification which could be uniform over the anterior lens or more dense centrally. At least half also had peripheral grey striae similar to those described by Bartholomew,[1] though he did

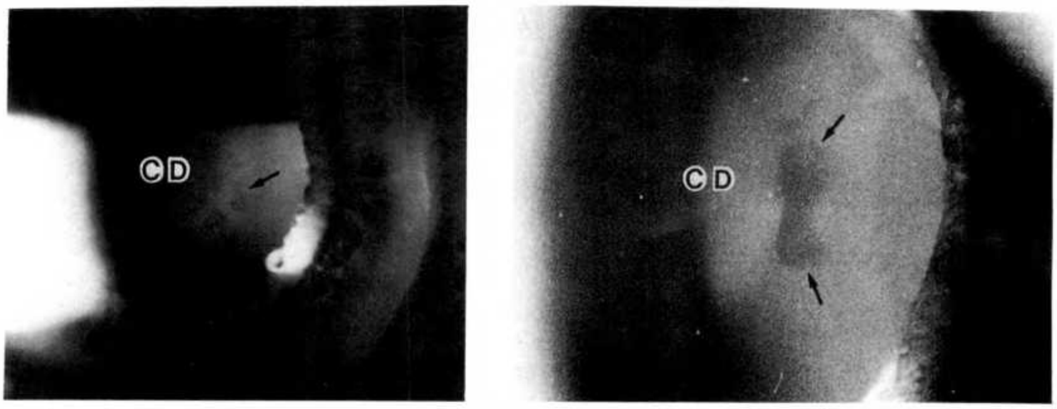


Figure 3 Anterior lens surface in two patients without evidence of pseudoexfoliative vegetations. Left: opacified precapsular film has several paracentral holes (arrows). Right: the central disc (CD) is denser, with a dumbbell-shaped hole at its edge (arrows).

not mention the presence of a diffuse film. A small number showed string-like shreds and nodules of rolled up PCF, and some had holes adjacent to the central area (Fig 3).

To determine the nature of the precapsular film we studied it on anterior lens capsules by light and electron microscopy.

Material and methods

Anterior lens capsules were obtained from 10 patients aged 65–80 undergoing capsulectomy for cataract extraction. These patients had previously given slit-lamp evidence of a PCF by showing peripheral grey striae on the midperipheral lens capsule, a more opaque central area, holes adjacent to the central area, or a combination of these findings. None had white vegetations characteristic of the granular phase of PSX. Specimens were fixed in 2·5% glutaraldehyde, dehydrated, and embedded in Mollenhauer's medium for transmission electron microscopy (TEM). Sections were stained with lead citrate and uranyl acetate. Capsulectomy speci-

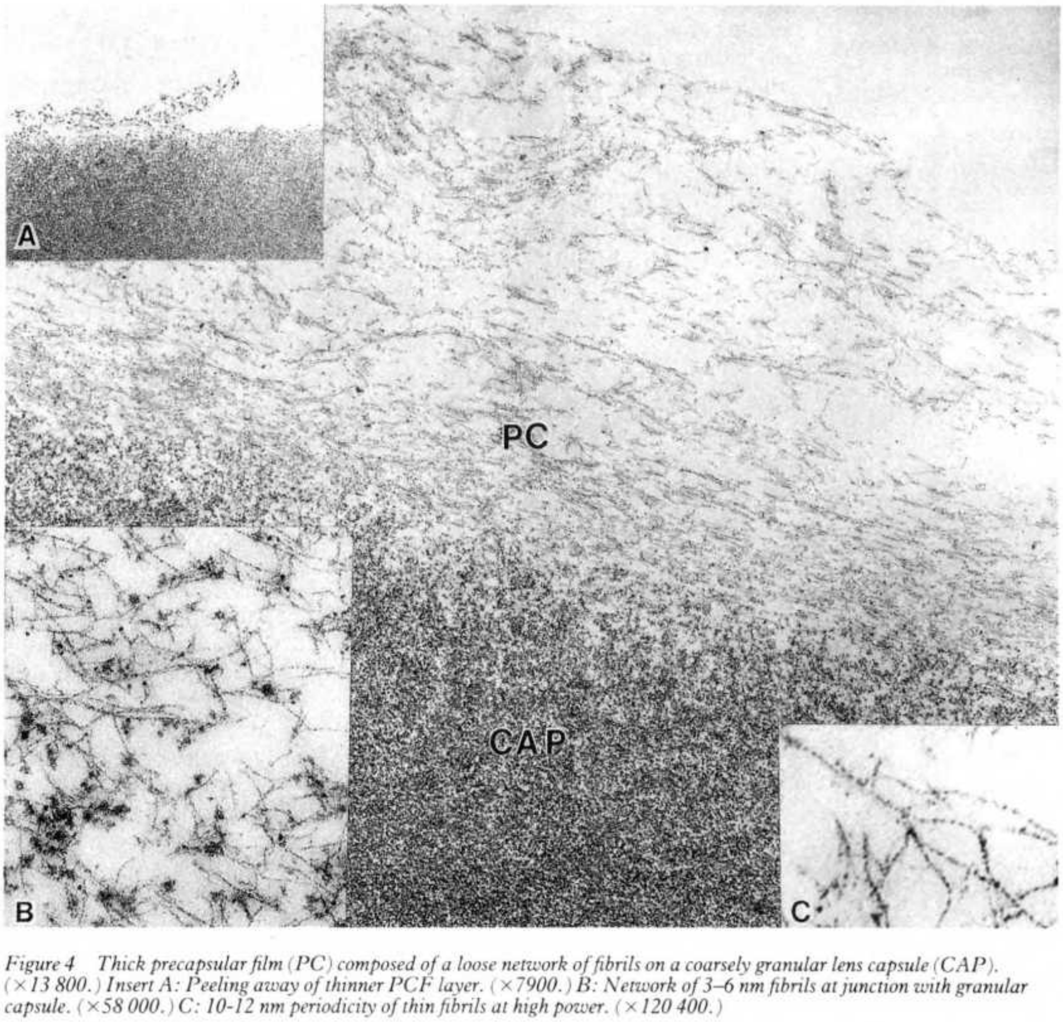


Figure 4 Thick precapsular film (PC) composed of a loose network of fibrils on a coarsely granular lens capsule (CAP). (×13 800.) Insert A: Peeling away of thinner PCF layer. (×7900.) B: Network of 3–6 nm fibrils at junction with granular capsule. (×58 000.) C: 10-12 nm periodicity of thin fibrils at high power. (×120 400.)

mens were obtained in the same way from 10 control patients in this age range who showed no preoperative evidence of PCF or PSX. All the patients in the study were examined preoperatively by one of us (AJD) and about two-thirds by both authors, residents, or other physicians, with concurrence on the clinical findings.

Four whole lenses noted to have PCF clinically were removed by intracapsular extraction. Three were examined by scanning electron microscopy after fixation in 2·5% glutaraldehyde, dehydration, and gold shadowing. The fourth lens was stained with monoclonal antibody to fibrillin,[3] a protein associated with elastic microfibrils and zonules, by the immunoperoxidase method before fixation, as previously described.[4] The capsule was then examined as a whole mount by light microscopy. Five lens capsules from normal eye bank eyes aged 16 to 83 years were similarly examined with fibrillin antibody as whole mounts.

Three lenses with clinical PSX disease were obtained by intracapsular extraction and fixed in 2·5% glutaraldehyde. Pieces from the central anterior capsule were prepared for TEM. Anterior capsules or whole capsules from three other PSX lenses were reacted with fibrillin antibody before fixation, and whole mounts were made for light microscopy, as described above.

Results

In all 10 capsulectomy specimens from patients in whom a PCF had been observed with the slit-lamp preoperatively, transmission electron microscopy revealed a layer of fine fibrils on the anterior capsular surface (Fig 4). The layer was 0·5–6 μm in thickness, tending to fragment and separate from the capsule. Pigment granules or other organelles were rarely noted interspersed among the fibrils. The fibrils were variable in length and 3–6 nm in width, with a suggestive periodicity of 10–12 nm at high power (Fig 4C). They were irregularly arranged but generally parallel to the surface and blended into the superficial capsule. Where the layer was thickest, the immediately underlying capsule was usually coarsely granular (Fig 4). Five of the 10 control capsules showed a relatively smooth fibrogranular anterior surface, without visibility of individual fibrils (Fig 5A). The other five control capsules showed some evidence of a fine fibrillar layer, though it was generally much thinner, patchy in distribution, and associated with amorphous material (Fig 5B).

By TEM the central disc region of established PSX showed a fibrillar layer on the anterior surface which was partly composed of 3–6 nm fibrils similar to those in the PCF (Fig 6). The texture was, however, looser, and embedded among the finer fibrils were typical thick PSX fibres up to 35 nm in diameter with a macroperiodicity of 45–55 nm. Also associated were some 8–10 nm fibrils with a 12 nm macroperiodicity, typical of zonular and other elastic microfibrils. The superficial capsule tended to be coarsely granular like that under the PCF.

By scanning electron microscopy (SEM) the lenses clinically showing a PCF had a superficial finely fibrillar layer of irregular outline (Fig 7), often having holes in it. Its edges were frequently peeled back or rolled into strings, which was doubtless artefactual, since it was not noted preoperatively, but showing the strong tendency of this thin layer to separate from the lens capsule. The fibrillar network was too fine to measure accurately by SEM.

Monoclonal antibody to fibrillin, an elastic microfibril-associated protein, was used to stain an entire lens capsule from a patient with a typical striated PCF. Besides staining zonular fibres and aging capsular inclusions in the usual fashion, the antibody bound to a fine network of loosely aggregated fibres on the anterior capsule central to the zonular insertion and blending into it peripherally. This network had an extensive but patchy distribution, tending to roll up at the edges or around eroded areas (Fig 8A).

By high power the fibres stained in a finely dotted pattern. In the mid zone the network

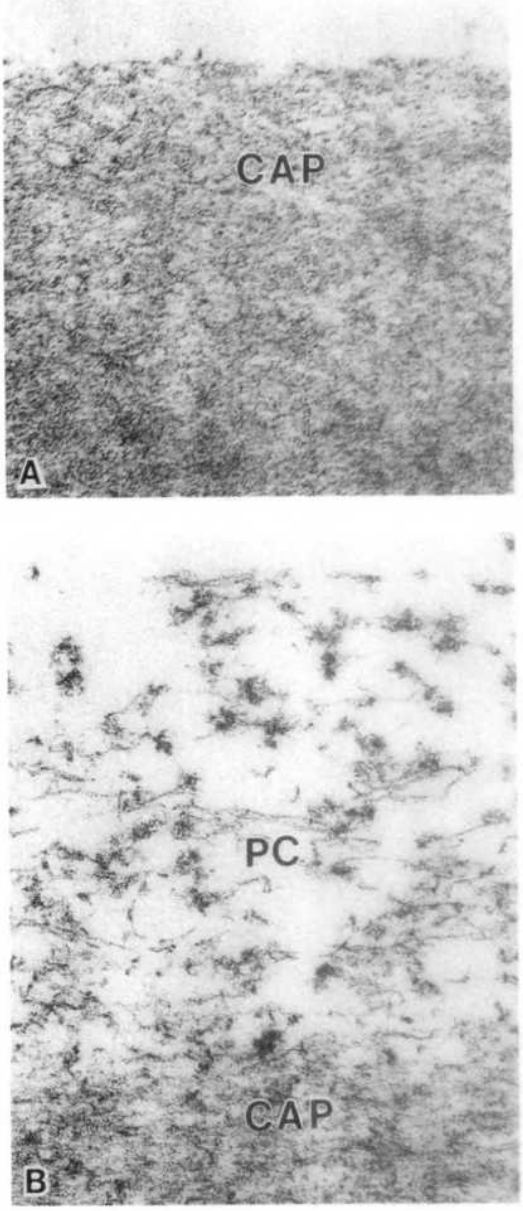


Figure 5 Anterior lens surface in controls A: Negative control with normal homogeneous fibrogranular capsular matrix. (×67 500.) B: Positive control showing fibrillar-amorphous precapsular film (PC). (×67 500.)

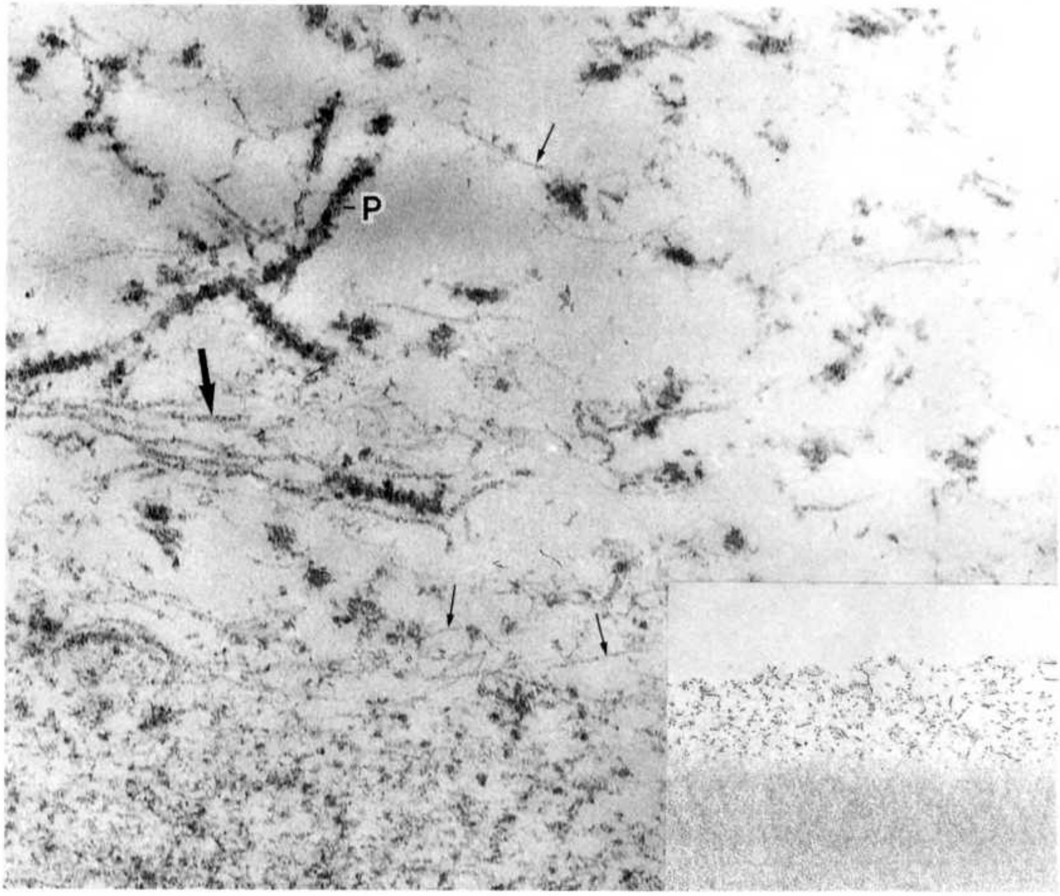


Figure 6 Fibrillar central disc on granular lens capsule in pseudoexfoliative disease. Fine 3–6 nm fibrils (thin arrows) intermingled with large coarsely banded PSX fibres (P), and 8–10 nm zonular-type periodic microfibrils (thick arrow). (×67 500.) Inset: Low-power view of this 0·3 μm layer, (×6150.)

showed a radial striate pattern, approximating in number and location to the grey striae seen clinically (Fig 8B). A similar pattern was seen more diffusely in the PSX lenses (Fig 8C), but there was also staining of the large PSX vegetations and deep fibrogranular zone. Control lenses had occasional wisps of fibrillin-staining network on the anterior capsule in patients over 40 years of age. The posterior capsule was unstained in all cases.

Discussion

The relucent or ground glass appearance of the superficial lens capsule we have noted in many older patients appears to correspond to the surface fibrillar network reported in the present paper, and called here the 'precapsular film'. The 3–6 nm fibrils composing most of the film are similar in size and morphology to the finer fibrils present in PSX vegetations, as well as on the surface and in the central disc area in established PSX disease.[5 6] We have shown that fibrillin, a glycoprotein closely associated with zonules and other elastic microfibrils,[3 4] is present in all areas of PSX aggregates on the lens capsule.[4]

The staining pattern for fibrillin in the surface network of PSX lenses and a PCF lens with radial striae was very similar. It is not possible to say whether the 3–6 nm fibrils represent more than one fibre type in either condition, but the findings suggest that PSX material and the striated film share at least one common antigen besides the ultastructural similarity of some of their fibrils.

The clinical behaviour of PCF films such as peeling, and the development of holes often surrounding a denser central zone, also resemble patterns seen in the intermediate zone of established PSX disease (Fig 1). Moreover, the presence of an almost complete PCF film in some patients with established PSX (Fig 2) suggests that the film could be the initial stage of the disease process. Gifford described a 'frosting' of the anterior lens capsule, without differentiating granular and pregranular phases, as the earliest finding in PSX, before hole development forms an intermediate zone.[7]

In studying PSX among the Bantu, Bartholomew[1] found that a peripheral grey striation of the anterior lens capsule formed initially, and PSX vegetations were deposited subsequently. We have frequently noted such striations in Caucasians clinically on both PCF and PSX lenses, and show here similar striations with fibrillin antibody. They may represent imprints from radial folds on the posterior iris surface, possibly more marked in some races such as the Bantu. Visualising these peripheral grey striae appears to be one method for determining the presence of a PCF. Similar striae were reported by Schläpfer[8] in 58% of glass factory workers, though in only 20% of clinic patients over 20 years of age. Bücklers[9] found some degree of striae in 77% of patients under 50 years of age

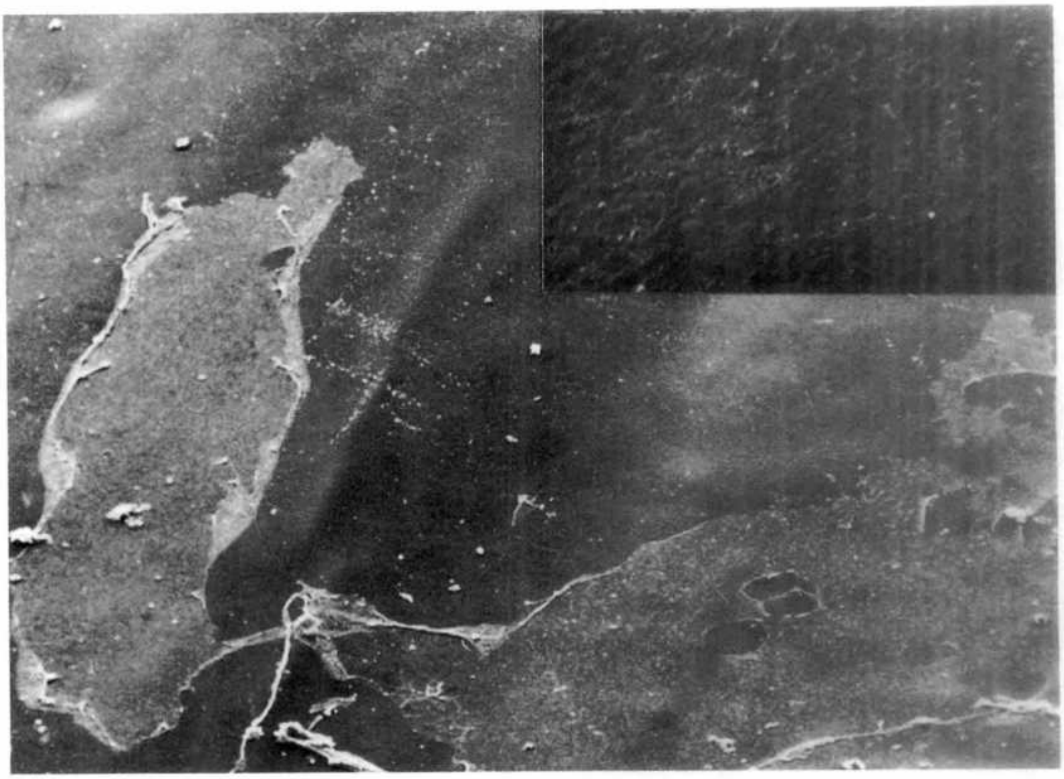


Figure 7 Scanning electron micrograph of anterior lens surface showing incomplete PCF eroded and rolled up at the edges, with string formation. From patient in Fig 3, right. (×70.) Inset: high power view of poorly defined fibrillar network. (×2500.)

and concluded that they represented a physiological change, though suggesting that they could be a forerunner of senile capsular erosion ('Abschilferung'). None of these reports describe a diffuse PCF, which may be a more specific sign of PSX disease.

Jerndal[2] found pigment deposits in the central and midperipheral zones of the anterior lens capsule at the initial biomicroscopic stage of pseudoexfoliation. He believed the pigment and subsequent exfoliation material derived from the iris pigment epithelium. We are aware that

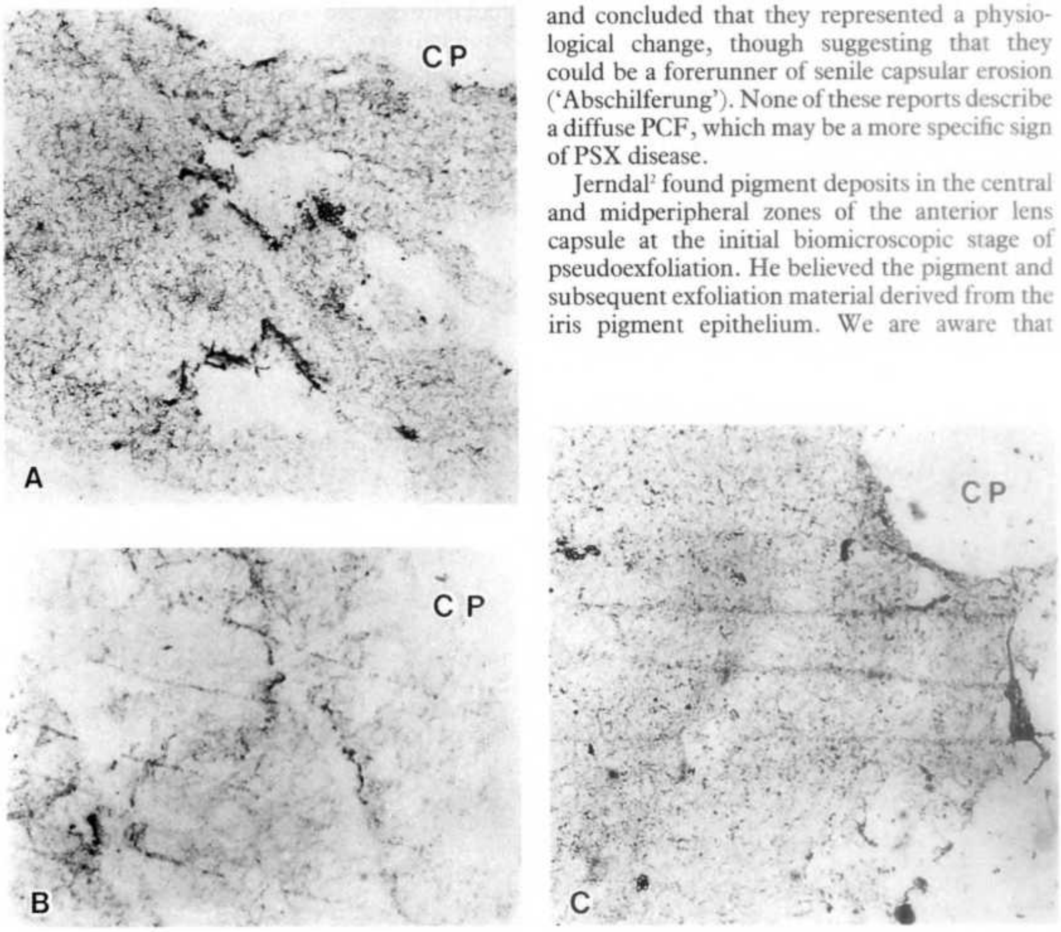


Figure 8 Anterior lens capsule reacted with fibrillin antibody. A: PCF shows a fibrillar network with focal holes on a non-staining capsule (CP). B: Faint radial striations in intermediate zone of a thin PCF. Capsule (CP) is unstained. C: More compact surface network in PSX disease showing striations, peeling and string formation on non-staining capsule (CP). (All immunoperoxidase, no counterstain ×500.)

pigmentary dispersion may be an early manifestation of PSX disease[10] and that pigment cells, their granules, and other organelles are a variable component of PSX material,[11,12] but did not find any regular pattern of pigment deposition in our patients.

An idiopathic exfoliation of the lens capsule was recently described in seven elderly patients,[13] one of whom had classical pseudoexfoliation. This condition appeared as a diaphanous membrane arising from the anterior lens capsule, protruding into the anterior chamber. It had some resemblance to the rolled up sheet-like material we depicted in the PCF by SEM, and what we have observed in some patients with PSX. An apparently unrelated transpupillary herniation of anterior lens capsule was recently noted in older peole in Somalia, strongly associated with climatic keratopathy but only weakly with established or classical PSX disease.[14] It is of interest that a white opalescence or 'frosting' of the central capsule was considered a precursor of these protrusions. Lacking a knowledge of the ultrastructure of these two disorders we are unable to speculate further on their possible relationship to the precapsular film described here.

The ultramicroscopic presence of some degree of PCF in half of our control lenses, though undetected clinically, indicates that in the cataract age group such aggregates are frequent. A sparse or optically uniform film would be naturally difficult to see clinically. In such instances Scheimflug photography coupled with densitometric image analysis might demonstrate it. It is possible that the PCF, which we have not noted clinically or ultrastructurally in younger eyes, may be a relatively common finding in aging, only progressing to PSX disease in some patients, or perhaps related only indirectly to PSX development. It is uncertain whether this surface film represents aberrant secretory products or material deriving from an aging lens surface, as the superficial capsule is often ultrastructurally abnormal as well. To understand this phenomenon, further knowledge about secretion and turnover of components in the zonular insertion-superficial lens capsular region is needed.

This work was supported in part by Research Grant EYO1602 from the National Eye Institute, National Institutes of Health.

1 Bartholomew RS. Pseudo-capsular exfoliation in the Bantu of South Africa. I. Early or pregranular clinical stage. *Br J Ophthalmol* 1971; **55**: 693–9.
2 Jerndal T. The initial stage of the exfoliation syndrome. *Acta Ophthalmol (kbh)* 1985; **173** suppl: 65–6.
3 Sakai LY, Keene DR, Engvall E. Fibrillin, a new 350-kD glycoprotein, is a component of extracellular microfibrils. *J Cell Biol* 1986; **103**: 2499–509.
4 Streeten BW, Gibson SA, Dark AJ. Pseudoexfoliative material contains an elastic microfibrillar-associated glycoprotein. *Trans Am Ophthalmol Soc* 1986; **84**: 304–20.
5 Dark AJ, Streeten BW. Pseudoexfoliation syndrome. In: Garner A, Klintworth GK, eds. *Pathobiology of ocular disease. A dynamic approach.* Part B. M. Dekker, New York. 1982; Pg. 1303–20.
6 Streeten BW, Bookman L, Ritch R, Prince AM, Dark AJ. Pseudoexfoliative fibrillopathy in the conjunctiva. A relation to elastic fibers and elastosis. *Ophthalmology* 1987; **94**: 1439–49.
7 Gifford H Jr. A clinical and pathologic study of exfoliation of the lens capsule. *Am J Ophthalmol* 1958; **46**: 508–24.
8 Schläpfer H. Neue Beobachtungen über Glasmacherkatarakt. *Klin Monatsbl Augenheilkd* 1930; **85**: 285–6.
9 Bücklers M. Die Strahlenkranztrubung ('Aureole'): eine physiologische Erscheinung an der Linsenvorderfläche. *Klin Monatsbl Augenheilkd* 1939; **103**: 413–7.
10 Prince AM, Streeten BW, Ritch R, Dark AJ, Sperling M. Preclinical diagnosis of pseudoexfoliation syndrome. *Arch Ophthalmol* 1987; **105**: 1086–2.
11 Dark AJ, Streeten BW, Cornwall CC. Pseudoexfoliative disease of the lens: a study in electron microscopy and histochemistry. *Br J Ophthalmol* 1977; **61**: 462–72.
12 Dark AJ. Cataract extraction complicated by capsular glaucoma. *Br J Ophthalmol* 1979; **63**: 465–8.
13 Cashwell FL, Holleman IL, Weaver GW, Gerrard H van R. Idiopathic true exfoliation of the lens capsule. *Ophthalmology* 1989; **96**: 348–51.
14 Johnson G, Minassian D, Franken S. Alterations of the anterior lens capsule associated with climatic keratopathy. *Br J Ophthalmol* 1989; **73**: 229–34.

A brighter start for dry eyes...

begins last thing at night

Used at night Lacri-lube soothes, protects and lubricates dry eyes for undisturbed sleep and comfort on waking.

LACRI—LUBE®
petrolatum mineral oil **OINTMENT**

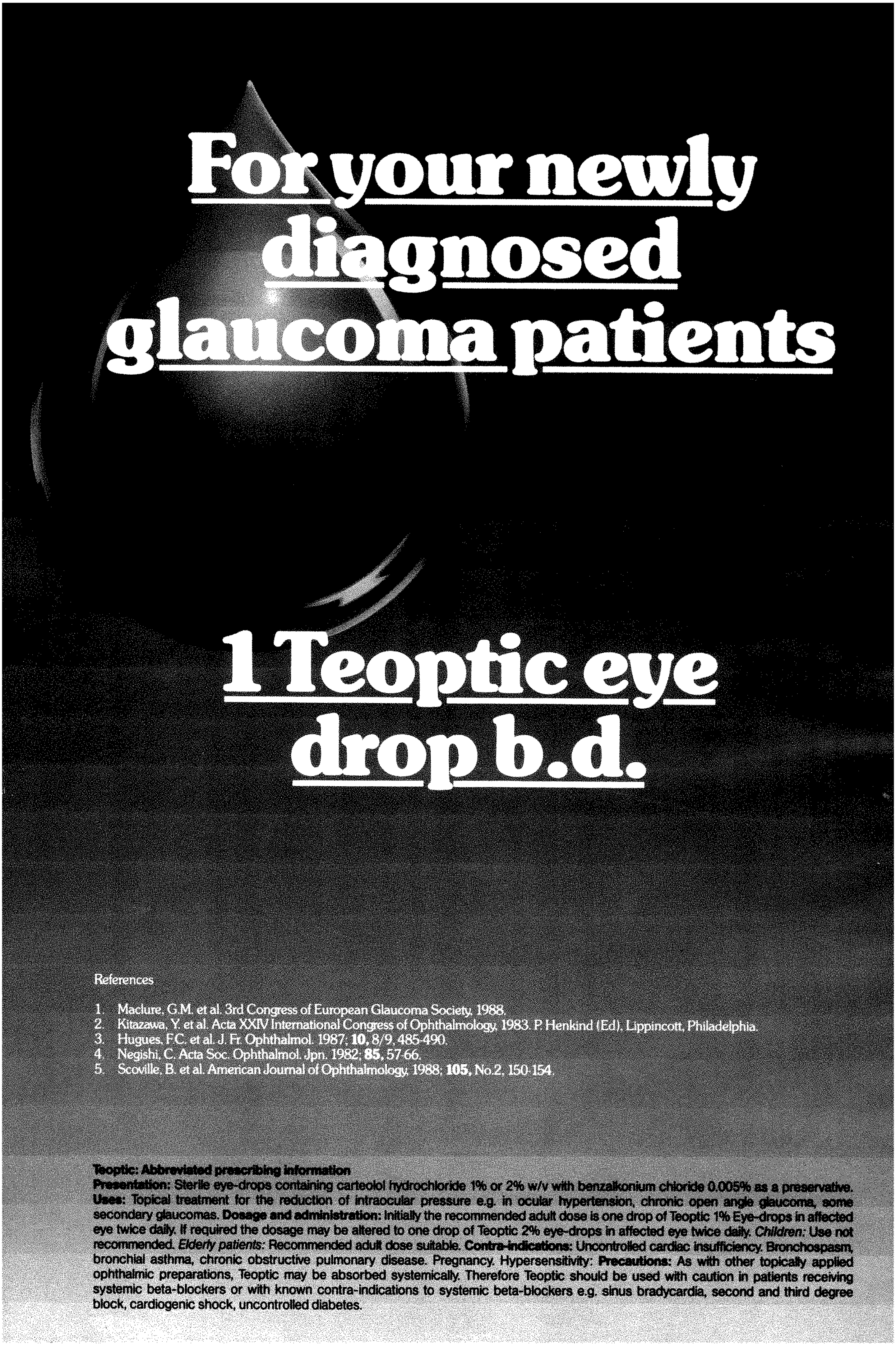
At the end of the day there's nothing quite like it for dry eyes

Lacri-Lube Prescribing Information. Presentation: Sterile, bland, non-medicated ophthalmic ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. **Uses:** Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. **Dosage and administration:** For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. **Contra-indications etc:** No known contra-indications. **Pharmaceutical precautions:** Store away from heat. To avoid contamination during use, do not touch tip to any surface. **Legal Category:** P. **Package quantities:** Available in 3.5g ophthalmic tubes. **Basic NHS Cost:** (as at May 1987) £1.76. **Product Licence Number:** PL 0426/0041. **Product Authorisation Number:** PA 148/38/1 (Allergan Pharmaceuticals (I) Limited, Westport, Co Mayo).

ALLERGAN PHARMACEUTICALS
TM
SCIENCE WITH VISION

Allergan Limited.
High Wycombe, Bucks. HP12 3SH

Full prescribing information is available on request. ®denotes registered trademark



References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10,** 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85,** 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105,** No.2, 150-154.

Teoptic: Abbreviated prescribing information
Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity. **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

TEOPTIC®

- Effectively lowers IOP [1]
- Has been shown to have less influence on pulmonary function, when compared with timolol and metipranolol * [2,3]
- Has a prolonged therapeutic effect [4] thus offering flexible b.d. dosage regimen
- Well tolerated with few local side-effects [5]
- Low concentration of benzalkonium chloride in a buffered solution.

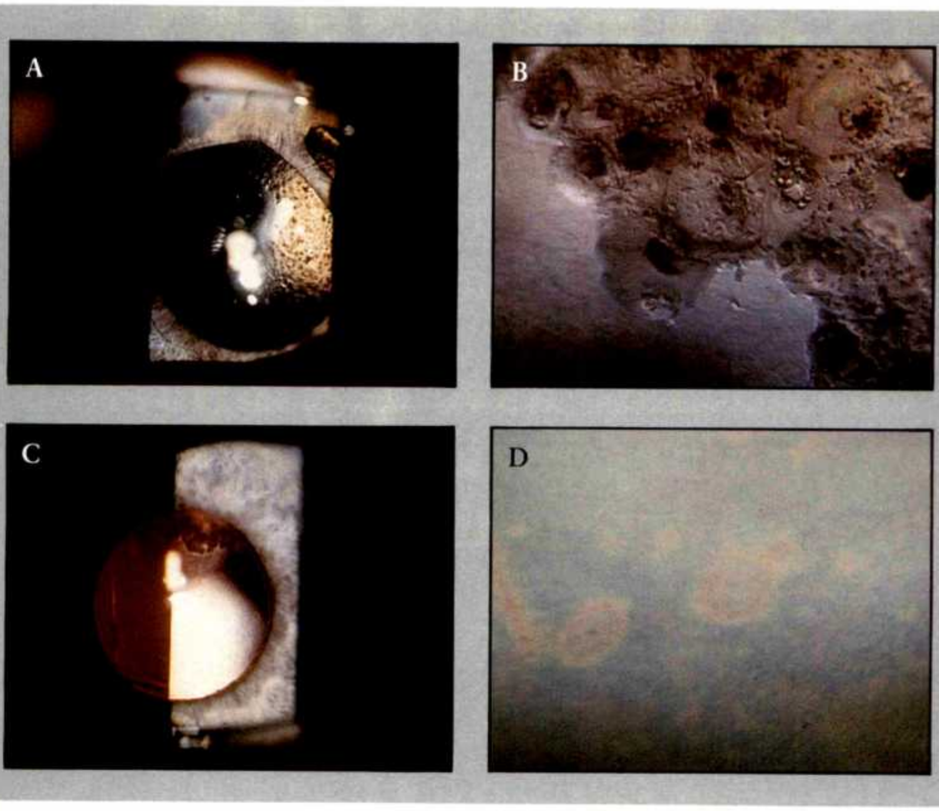
* Even though Teoptic may be less likely to induce airways narrowing when compared with timolol and metipranolol, its use is contra-indicated in patients with a history of bronchospasm.

Teoptic®
carteolol hydrochloride
eye drops

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic N.H.S. Cost and Product Licence Numbers:** Teoptic 1% eye-drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% eye-drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP.

Teoptic is under licence from Otsuka, Japan. Further information is available on request to the above address.

Comparison between Heparin surface modified IOLs and normal IOLs in the same patient.



This female has a history of longstanding diabetes and glaucoma.

A. Slit lamp
B. Specular microscopy

Right eye — NORMAL PMMA LENS

- 11 months post-operative
- Confluent giant cells can seen clearly on both slides

C. Slit lamp
D. Specular microscopy

Left eye — HEPARIN SURFACE MODIFIED LEN

- 6 months post-operativel
- No giant cells
- Newton's rings seen clearl

A clear case for Heparin surface modified IOLs.

Pharmacia Limited,
Ophthalmics Division, Pharmacia House, Midsummer Boulevard, Milton Keynes MK9 3HP.
Telephone: (0908) 661101. Telex: 826778. Fax: (0908) 690091

Pharmaci

British Journal of Ophthalmology, 1990, 74, 723–730

Pathogenesis of corneal oedema associated with herpetic eye disease

William J O'Brien, Julie Guy, Jerry L Taylor

Departments of Ophthalmology and Microbiology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
W J O'Brien
J Guy
J L Taylor

Correspondence to:
W J O'Brien, PhD, Eye Institute, Room 826, Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, WI 53226 USA.

Accepted for publication
21 June 1990

Abstract

Corneal oedema and stromal disease, induced in rabbits by intrastromal injection of herpes simplex virus, type 1, strain RE (HSV-1, RE), reached a peak of 12–15 days after infection. Corneal oedema as measured by ultrasonic pachymetry, and stromal disease as measured by a subjective scoring system, were closely related for 30 days after infection. Morphometric analysis of wide field specular micrographs showed that no immediate endothelial cell damage occurred in either control or HSV-1 infected corneas. Alizarin red S staining of corneas taken during the period of most severe oedema indicated no significant endothelial cell loss; however, visual inspection indicated numerous staining abnormalities. Scanning and transmission electron microscopy provided evidence of an intact endothelial layer possessing integrated infiltrating cells. Virus antigen could not be detected on endothelial cells by immunoperoxidase staining at any time during development of corneal oedema. The results indicate that corneal oedema associated with HSV-1 induced disease can occur in the absence of detectable virus replication and cytolysis of corneal endothelial cells.

Corneal oedema is associated with numerous manifestations of herpes simplex virus type 1 (HSV-1) induced ocular disease.[1] Oedema may develop with the progression of acute disease into the corneal stroma when infection is produced by strains of HSV-1 which have a strong tendency to produce stromal disease.[2] Disciform corneal oedema may follow acute corneal infection or appear during recrudescence in the presence or absence of obvious epithelial disease.[3] Corneal oedema is often a significant feature of keratouveitis produced by HSV-1 infection.[4]

The oedema produced in association with these varying forms of HSV ocular disease may spontaneously resolve or persist and contribute to the development of chronic stromal disease and necrotising stromal keratitis.[5] The pathophysiological mechanisms responsible for the corneal oedema associated with this spectrum of HSV induced diseases are unknown. However, one would anticipate that the corneal endothelium, as a major regulator of water balance in the cornea, would have a central role. Sundmacher[6] has proposed that disciform oedema, for example, represents a viral disease of the endothelium involving replication of the virus in the endothelium followed by attack of immunocompetent cells on infected endothelial cells, the latter being more harmful to the endothelium. However, little direct evidence exists to confirm the presence of virus or viral antigen in the endothelium during the course of disease.

Virus has been cultured from the anterior chamber of patients with endotheliitis, but the site of replication was not positively established.[7] The literature contains other reports of endothelial defects including endothelial cell loss associated with herpes virus induced anterior segment disease.[4,8,9] Clinically, however, it is often difficult to evaluate the condition of the endothelium during disease because in many cases corneal oedema interferes with slit-lamp examination and specular microscopy. In addition, the source of virus cannot be positively identified without enucleation and careful study of the ocular tissues.

Animal experiments have provided some important information on the state of the corneal endothelium in HSV induced disease, though the mechanisms responsible for corneal oedema have not been well characterised. The injection of live virus into the anterior chamber of rabbit eyes results in the apparent replication of virus in corneal endothelial cells and corneal oedema.[10,11] Growth of virus has been observed in cultures of HSV infected rabbit corneal endothelial cells[12,13] (O'Brien *et al*, unpublished data). Movement of virus to endothelial cells and replication in those cells may reflect both a strain dependent character of the virus and the immune status of the host. Spread of virus from an epithelial site of inoculation to the endothelium occurs with some strains of HSV-1, while other strains do not disseminate or require corticosteroids to promote spread of virus to the endothelium.[11] Irvine and Kimura[14] demonstrated that topical inoculation of the rabbit cornea with the RE strain of HSV-1 induced 'non-specific' morphological damage to the endothelium as asessed by coelestine blue staining. Virus was cultured from endothelial cell scrapings prior to but not during the time of maximal corneal pathology. Owing to the nature of the culturing technique the source of virus could not be positively identified. In contrast to these studies other studies indicate that during periods of most severe inflammation virus antigens are rarely found in the endothelium following topical epithelial infection of the rabbit unless immunosuppressive agents are given.[15]

In the studies reported here intrastromal injection of the RE strain of HSV-1 resulted in the development of corneal oedema in rabbits peaking at a time after epithelial lesions were nearly healed and virus could not be detected in tears. The data show that stromal disease, as evaluated by the subjective scoring system devised by McNeill and Kaufman,[16] correlates closely with corneal thickness as measured by pachymetry during the first 30 days after infection. In the oedematous corneas no virus or viral antigen could be detected by transmission electron microscopy or immunocytochemistry. Corneal endothelial cell numbers and morphometric parameters such as hexagonality were not significantly altered during development and recovery from oedema, though many abnormalities in alizarin red staining were observed. At the time of maximal thickness what appeared to be inflammatory and immune cells were found integrated within the endothelial layer. The results show that corneal oedema can be induced after actue stromal and epithelial disease in the absence of viral cytolytic destruction of the endothelium.

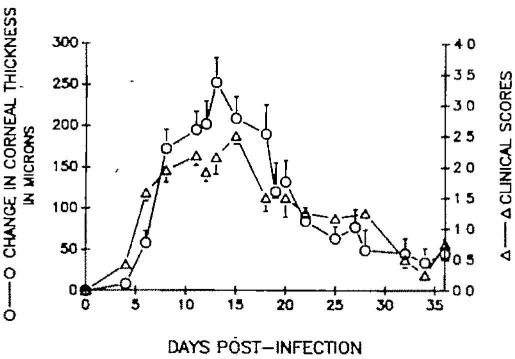


Figure 1 Kinetics of development in stromal disease (Δ) and oedema (O) after intrastromal injection of HSV-1. Each data point represents the mean with the standard error of the mean. On days 0 through 8 (n=30 eyes), days 11 through 18 (n>14<22), and days 20 through 36 (n=10).

Material and methods

HERPES SIMPLEX VIRUS CORNEAL INFECTIONS

Specific pathogen-free male New Zealand white rabbits (2·3–2·7 kg) (Hazleton Research Products, Denver, PA) free of pre-existing corneal defects were infected bilaterally by intrastromal injection of 20 µl of phosphate buffered saline (PBS) containing 10^3 plaque forming units (pfu) of the RE strain of HSV-1.[17] Control rabbits received intrastromal injections of 20 µl of the same dilution of mock antigen prepared from uninfected RK-13 cell lysate.

CLINICAL ASSESSMENT OF DISEASE

At selected daily intervals before and after infection, rabbits were anaesthetised by intramuscular injection of 5 mg of ketamine hydrochloride and 10 mg of xylazine. Corneal thickness was measured by use of an ultrasonic pachymeter (DGH Technology Inc, Frazer, PA) which was calibrated for use on rabbit corneas. Central corneal thickness was taken as the mean of three measurements for each cornea.

The severity of corneal stromal disease was graded on a 0 to 4 scale by means of a slit-lamp.[16] Briefly, grading of disease severity was based on corneal clarity (0=clear cornea with iris details distinctly visible; 1=detectable oedema with iris details clearly visible; 2=gross oedema with iris details still distinctly visible; 3=gross oedema with iris details and pupillary border no longer distinctly visible; 4=opaque cornea with iris details not visible). Corneal epithelial disease was graded on a 0 to 4 scale following fluorescein staining (0=no stain; 1=25% of the corneal surface stained; 2=50% staining; 3=75% staining; 4=100% staining). Wide field specular micrographs were taken before and for up to three days after injection with a Keller-Konan specular microscope (Keeler Instruments, Inc, Broomall, PA) on Kodak Tri-X film which was developed and printed for morphometric analysis.[18] Clusters of 100 individual cells were digitised and subjected to computer analysis to calculate cell density, cell area, coefficient of variation of cell area, and percentage of hexagonal cells.[19]

Table 1 Morphometric parameters of the corneal endothelium following intrastromal injection mean (with SEM)

Days after injection	*HSV**	*Cells/mm²*	*Mean cell area* (µm²)	*Coeff. var*†	% Hexagons	n‡
6	–	4128 (260)	244 (15)	16 (1)	71 (1)	3
	+	3652 (205)	279 (16)	18 (1)	71 (3)	6
12	–	3626 (348)	277 (8)	16 (1)	71 (3)	3
	+	3834 (147)	262 (10)	23 (2)	73 (3)	5
18	–	3989 (192)	252 (12)	22 (2)	66 (1)	3
	+	3828 (321)	265 (24)	18 (1)	67 (2)	3
27	–	3828 (131)	262 (9)	19 (1)	67 (2)	4
	+	3477 (146)	289 (12)	17 (1)	68 (3)	4

*–Indicates control corneas receiving injections of mock antigen preparation; +indicates HSV infected corneas †Coefficient of variation of the mean cell area ‡Number of micrographs from different eyes which were digitised.

ALIZARIN RED S STAINING

At selected intervals following intrastromal injection rabbits were killed by intravenous injection of sodium pentobarbital and the corneas excised with a scleral rim. Flat mounts of whole corneas were prepared with the endothelial surface upwards so that the cell junctions would stain with alizarin red S as described by Taylor and Hunt.[19] The stained endothelial flat mounts were photographed, prints prepared, and morphometric analysis performed.[20]

PEROXIDASE/ANTIPEROXIDASE STAINING

A modification of the technique described by Shimeld *et al*[21] was used to stain corneal endothelial flat mounts for the presence of HSV-specific antigens by the immunoperoxidase technique. Corneas were excised with 2–3 mm of scleral rim at various times after intrastromal injection and fixed with Bouin's solution for 12 h. Each cornea was rinsed in 50% ethanol and stored in 70% ethanol until staining. Prior to staining the corneal tissues were rehydrated, and a 10 mm central corneal button removed by trephination. The endothelium with a small amount of stroma was removed by stripping with forceps. The endothelial layers were mounted on slides and dried under coverslips at room temperature. The tissues were treated with 4·8% hydrogen peroxide in methanol, washed in phosphate buffered saline (PBS), and treated with normal goat serum (Calbiochem, La Jolla, CA). Tissues were then sequentially treated with appropriate dilutions of guinea-pig anti-HSV-1 antiserum (Bethesda Research Products, Bethesda, MD), affinity purified goat anti-guinea-pig IgG (Jackson Immuno-Research

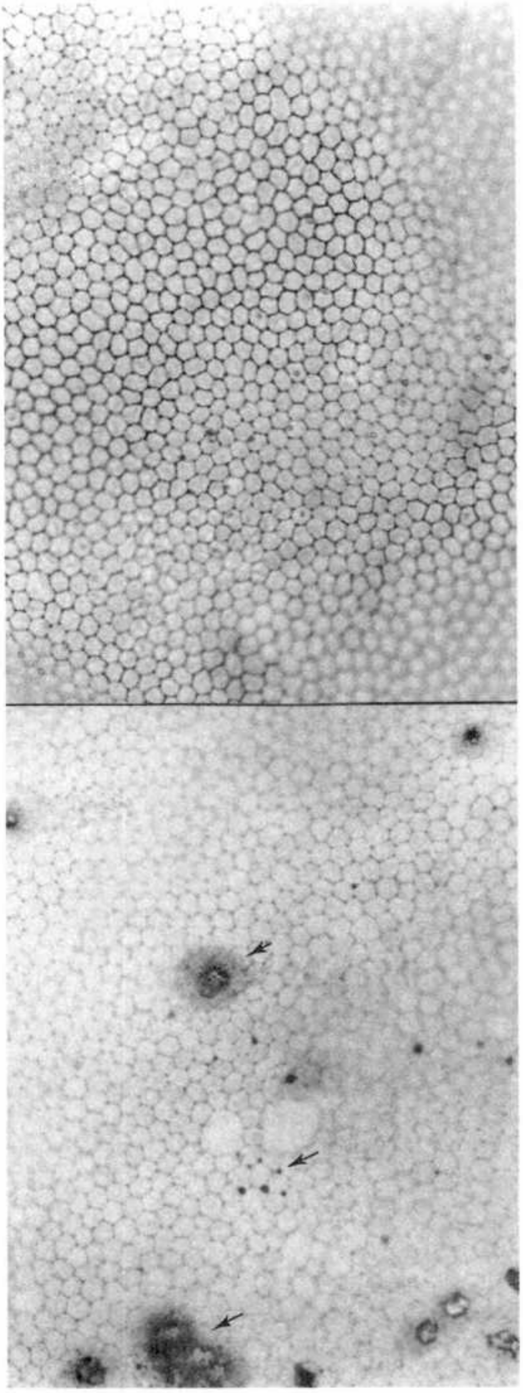


Figure 2 Alizarin red S stained flat mounts of the corneal endothelium of mock antigen-injected control eyes (top) and HSV-infected eyes (bottom) prepared 12 days after infection. Examples of staining abnormalities are indicated by arrows. (Original magnification ×132.)

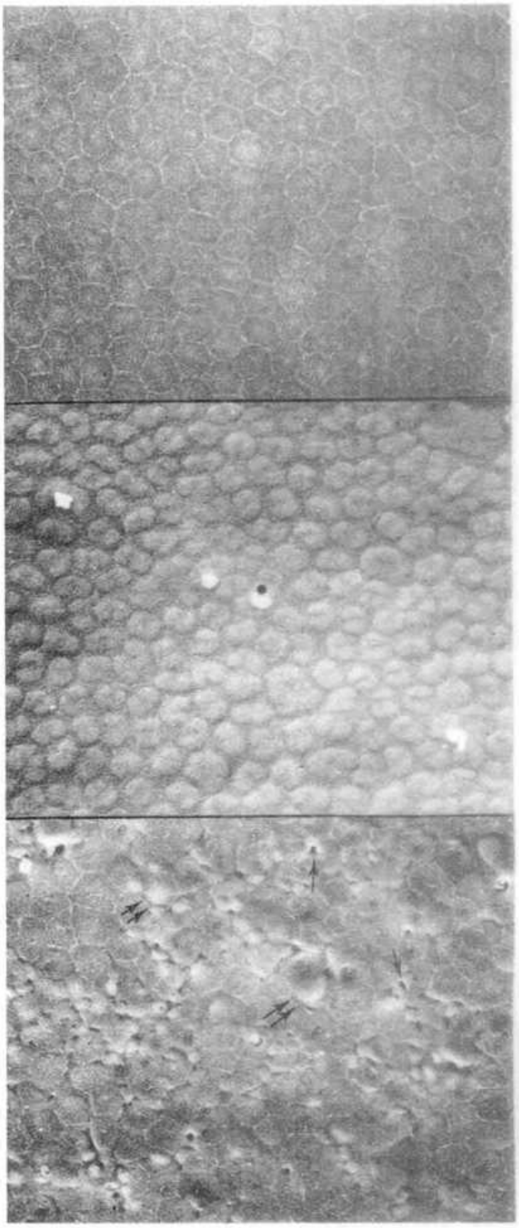


Figure 3 Scanning electron micrographs of corneal endothelium of mock-antigen-injected control corneas (top), HSV-infected corneas six days after infection (centre), and 12 days after infection (bottom). Infiltrating cells on endothelial surface (*), junctional gaps (single arrows) and an area containing infiltrating cells within the endothelial cell layer (double arrows) were observed. (Original magnification × 500.)

Laboratories, West Grove, PA), and guinea-pig peroxidase/antiperoxidase complex (Jackson Immuno-Research Laboratories, West Grove, PA). Coloured reaction product was detected by reaction with 0·05% diaminobenzoic acid in Tris-HCl buffer (pH 7·6) containing 0·03% hydrogen peroxide. Tissues were rinsed and a coverslip placed over them for observation.

MICROSCOPY

For scanning electron microsopy of the endothelium corneas were excised, fixed in 2·7% glutaraldehyde in phosphate buffer (pH 7·6), postfixed in 2% osmium tetroxide, mounted on stubs, and sputter coated with gold-palladium.[22] Corneal tissues examined by scanning electron microscopy were removed from scanning electron microscopy mounts with acetone and immersed in propylene oxide to remove the gold-palladium coating. Each cornea was cut into segments and the segments were embedded in Spurr's low viscosity epoxy resin (Polysciences Inc, Warrington, PA). Sections (1 μm were cut, mounted on microscope slides, and stained with toluidine blue for light microscopy. Thin sections were cut from the same blocks, stained with uranyl acetate and lead citrate, and mounted on grids for transmission electron microscopy (TEM).[22]

All numerical data are reported as the mean with standard error of the mean. Student's *t* test or paired *t* test were used where appropriate to compare data of various groups.

Results

CLINICAL ASSESSMENT

The eyes of 15 rabbits were infected by intrasomal injection of 10^3 plaque forming units (pfu) of the RE strain of HSV-1. The progression of corneal disease was followed by slit-lamp examination and ultrasonic pachymetry. Corneal stromal disease as assessed by the subjective grading scheme of McNeill and Kaufman[16] reached maximum about 12–15 days after infection (Fig 1). The measured corneal thickness similarly reached a maximum in that time frame (Fig 1). Subjective clinical evaluation and the actually measured corneal thickness showed a close relationship for 27 days after infection. Corneal epithelial disease in HSV infected rabbits as measured by fluorescein staining progressed steadily to a maximum score (1·1 (SEM 0·2) n=30) by eight days after infection and was nearly resolved by day 12 after infection (0·2 (SEM 0·1), n=15). Control rabbits receiving 20 µl injections of equivalent dilution of mock antigen showed no significant increase in corneal thickness (384 (SEM 4) µm, n=16) or stromal disease (0·1 (SEM 0·2) n=16) on day 13 after injection. These data predict that endothelial dysfunction or abnormality would be the greatest during the period 12–15 days after infection.

MORPHOMETRIC ANALYSIS OF THE CORNEAL ENDOTHELIUM

To insure that intrastromal injection of 20 µl of either virus or mock antigen diluted in Hank's balanced salt solution did not cause direct cell damage, the endothelium was examined by contact specular microscopy. Eight eyes of randomly selected rabbits were photographed prior to injection and one day after injection. Prior to injection the endothelial layers contained 3513 (SEM 76) cells/mm^2 with a mean area of 286 (SEM 6) µm^2/cell having a coefficient of variation of 18 (SEM 2)%, and 71 (SEM 2)% of the cells were hexagons. One day after injection the central corneal endothelium in the area of the injection site contained 3414 (SEM 79) cells/mm^2 with a mean area of 294 (SEM 7) µm^2/cell having a coefficient of variation of 20 (SEM 3)% and 72 (SEM 2)% hexagons. A paired *t* test showed no significant cell loss or other abnormalities, so that the injection procedure did not appear to result in endothelial cell damage.

Corneal thickness began to increase significantly by days 6–8 after infection, so clear, useful specular microscopic images of the endothelium were nearly impossible to obtain. We therefore assessed all endothelial morphometric parameters by preparation of alizarin red S stained flat mounts. The preparation and analysis of flat mounts of this nature are useful in obtaining morphometric analysis. However, owing to about 14% shrinkage, the apparent cell number is increased by about 14%.[20] Morphometric analysis of the corneal endothelium of mock-antigen-injected controls and HSV-1-infected corneas indicated that no significant loss of endothelial cells occurred either during the development or recovery from HSV-1 induced corneal oedema and stromal disease (Table 1). Similarly, because no significant change was observed in the coefficient of variation of cell size or the percentage of cells remaining as hexagons, there is no evidence of recent major endothelial cell loss in the vicinity of the areas digitised.[18]

The alizarin red-stained endothelial flat mounts taken during the period of maximal corneal thickness did show many staining abnormalities. The endothelium of corneas receiving injections of mock antigen displayed a normal staining pattern (Fig 2, top). The flat mounts of HSV-1 infected corneas, however, had numerous defects, including areas of pooling of stain at the cell vertices, areas of diffuse stain, areas of intense stain, and areas where the staining pattern of the endothelial cell borders was no longer visible (Fig 2, bottom). In the latter case it was difficult to determine the exact cause of the loss of the normal staining pattern. In many cases small areas appeared in which the normal staining pattern was faint but intact and obscured by debris or cells sitting on or within the endothelial layer.

SCANNING ELECTRON MICROSCOPY

In order to observe better the nature of the defects in the corneal endothelium, corneas of control and HSV-1 infected rabbits taken during each of four time periods were examined by scanning electron microscopy. Control corneas taken 6–8 days, 12–16 days, 18–20 days, and 30–37 days after injection of mock antigen showed few obvious defects (n=3 during each time

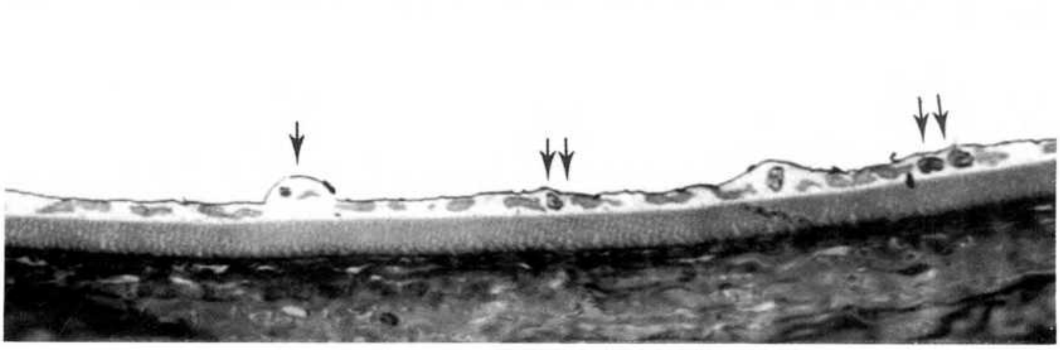


Figure 4 Toluidine blue-stained sections showing the endothelium prepared from HSV infected corneas taken 12 days after infection. Infiltrating cells were attached to the endothelial layer as indicated by the arrow (left) and incorporated within the layer as shown by the arrows (right). (Original magnification ×132.)

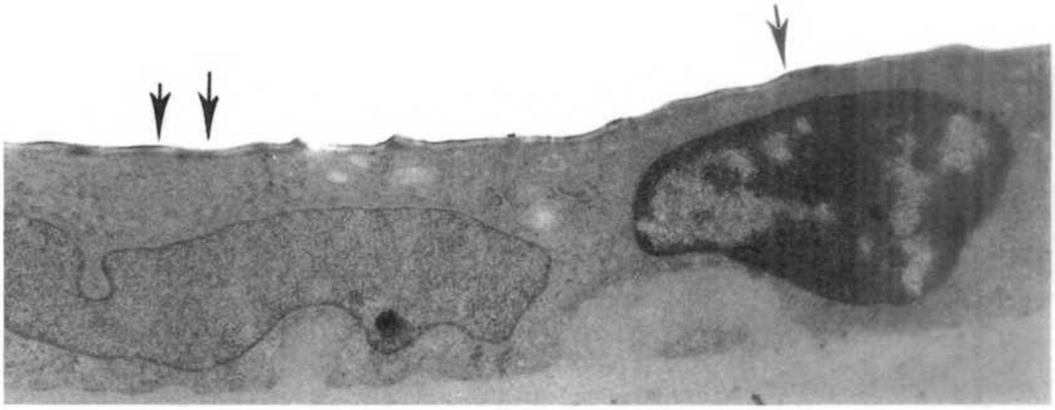


Figure 5 Transmission electron micrograph shows the corneal endothelium from an HSV-1 infected rabbit 12 days after infection with an unidentified infiltrating cell (arrow) within the endothelial cell layer and adjacent to an endothelial cell (double arrows). (Original magnification ×5000.)

period) (Fig 3, top). HSV infected corneas taken early in the course of development of stromal disease and oedema (6–8 days after infection) appeared to possess inflammatory cells in or on a normal endothelial cell layer (n=6) (Fig 3, centre). At severe stages of oedema numerous endothelial defects appeared, including junctional gaps and infiltration of the cell layer; however, major areas of endothelial cell loss were not observed (n=5) (Fig 3, bottom).

In random electron micrographs taken at magnification ×200 and evaluated in a masked fashion the number of defects per field increased significantly in the HSV infected rabbits from 1·8 (SEM 0·9) defects/field (n=4) at days 6–7 after inoculation to a maximum of 27·6 (SEM 17·9) (n=3) at days 12–14, about the time of maximum corneal thickness. Numbers of defects then gradually decreased, with 6·8 (SEM 2·6) (n=4) at 18–20 days after infection and returned to 3·0 (SEM 2) (n=3) after 30–37 days. Corneas from control animals taken at each of these time points showed no comparable defects.

LIGHT AND TRANSMISSION ELECTRON MICROSCOPY

In an effort to understand better the nature of the endothelial defects in the corneas observed by SEM the specimens were uncoated, reblocked in epoxy resin, and sectioned for both light and TEM. Observation of these specimens by light microscopy following toluidine blue staining suggested that the irregularities in the endothelium during the period of maximum corneal oedema were due to infiltration of the endothelial layer with inflammatory cells and lymphocytes (Fig 4). Early in the course of oedema (6–8 days after infection), cells were frequently observed attached to the luminal surface of the endothelium. As oedema became more severe, TEM indicated that infiltrating cells were incorporated within the endothelial layer, especially during the period of maximal corneal oedema (Figs 5, 6, 7). Many of the cells had large areas of rough endoplasmic reticulum typical of plasma cells (Fig 7). Cells were not observed within or spanning Descemet's membrane. Cells and flare in the anterior chamber were rarely observed at any stage of disease. An intense anterior chamber reaction characterised by the development of hypopyon was not characteristic of the disease studied.

Virus particles were not detected by TEM in any endothelial cell layers observed (4–6 corneas

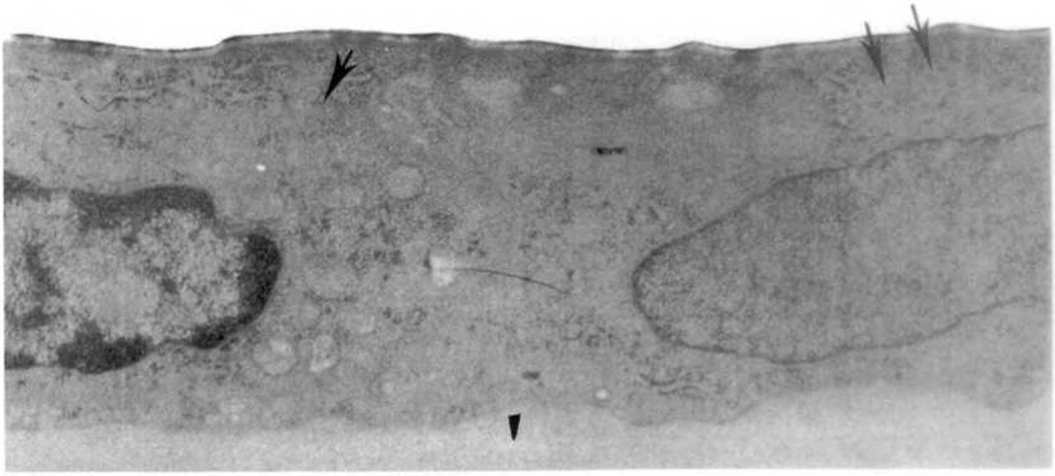


Figure 6 Transmission electron micrograph shows an unidentified infiltrating cell (arrow) incorporated within the endothelial cell layer adjacent to an endothelial cell (double arrows) in the cornea of an HSV-1 infected rabbit 14 days after infection. (Original magnification ×8000.)

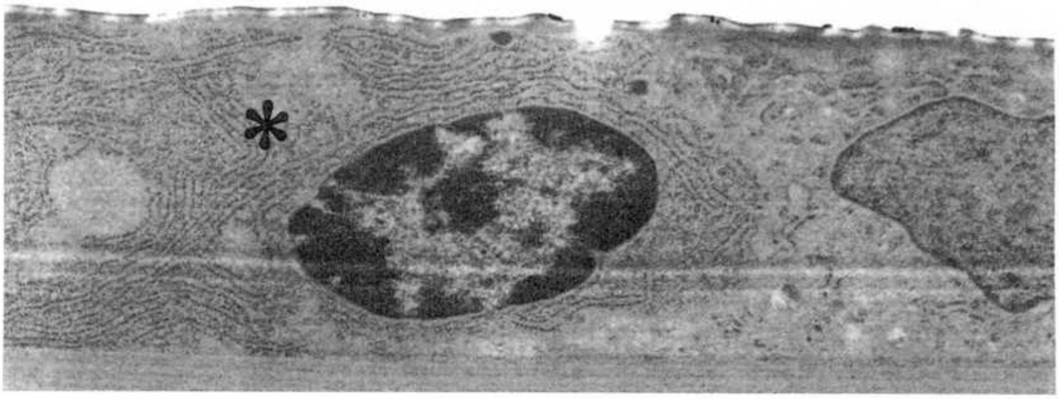


Figure 7 Transmission electron micrograph of a plasma cell (asterisk) adjacent to an endothelial cell in the cornea of an HSV-1 infected rabbit 12 days after injection. (Original magnification ×5000.)

examined per time point, four blocks per cornea, 6–10 sections per block). Sections of corneas taken at each time period from six days after infection to 36 days after infection showed no evidence of replicating virus in the endothelium. Virus particles were found with ease in the epithelium and stroma from corneas taken six days after infection. The presence of non-enveloped particles within the nuclei and enveloped particles in the cytoplasm suggested that virus was replicating in both stromal and epithelial cells. By day 12 after infection virus particles became increasingly difficult to locate in these cells until by days 30–36 after infection virus was not observed in any corneas.

IMMUNOPEROXIDASE DETECTION OF HSV-1 ANTIGEN

Endothelial flat mounts of Bouin's fixed corneas were prepared from each of the groups of rabbits studied to detect the presence of viral antigen. Monolayers of Vero cells and organ cultured corneas were infected in vitro to serve as antigen-positive control. Peroxidase reaction product was readily visible in positive controls and was not visible in virus negative controls. None of the eight endothelial layers examined from infected rabbits taken 6–8 days after infection or the nine corneas taken during the period of maximum oedema possessed peroxidase-positive endothelial cells. Corneas taken after day 12 after infection often contained peroxidase-positive cells, thought to be plasma cells (Fig 8). These cells appeared with greatest frequency during the 12–18 day period after infection and decreased but were still occasionally present in some endothelial preparations as late as 36 days after infection. Immunoperoxidase-positive cells were not observed in mock-antigen-injected control cultures.

Discussion

Corneal oedema is associated with a diversity of clinical presentations of ocular HSV infections. Dysfunction of the corneal endothelium is the presumed source of oedema, but more than one mechanism may lead to this dysfunction. We have shown that the RE strain of HSV-1 used in these studies does not readily disseminate within the cornea to infect the endothelium. Alizarin red S staining and scanning electron microscopy indicate that, although defects could be detected, the corneal endothelial cell layer remains basically intact. Nevertheless corneal oedema is a significant feature of the disease, and its appearance closely correlates with the clinical evaluation of severity of stromal disease and infiltration of inflammatory and immune cells into the endothelium. Under these conditions of inflammation and oedema neither virus nor viral antigens were found in association with the corneal endothelium. While it is possible that the levels of virus and viral antigen are below the level which we can detect, the presence of an endothelium devoid of large areas of cell destruction makes it unlikely that the endothelial cells are a principal site of virus replication. Therefore with the strain of HSV used in these studies even after intrastromal injection oedema occurs, but the virus does not appear to move to the endothelium.

Infection of rabbits with other strains of virus which can disseminate in the cornea to the endothelium appears to produce oedema by a second mechanism. Infection of endothelial cells followed by cell lysis could clearly compromise endothelial barrier function. In animal experiments virus has been observed to infect endothelial cells after direct injection into the anterior chamber of rabbits,[10 11] and selected isolates of some strains of virus such as McKrae and RE appear to be capable of spreading to the endothelium.[11 14] In the latter case the data provided do not definitely identify the corneal endothelial cells as supporting virus replication.

Data from patients are limited by the inability to obtain samples or visualise the endothelium during severe oedema. While virus isolation from the anterior chamber has been reported, the source of virus has not been positively identified as endothelial cells.[7]

Direct observation of the endothelium of some patients with HSV induced disease has provided suggestive evidence of focal endothelial cell loss, but the cause of the apparent cell loss cannot be directly establshed.[4 8 9] Other endothelial cell abnormalities in the form of multinucleate giant cells and increased mean cell area have been observed in one patient with a 12-year history of

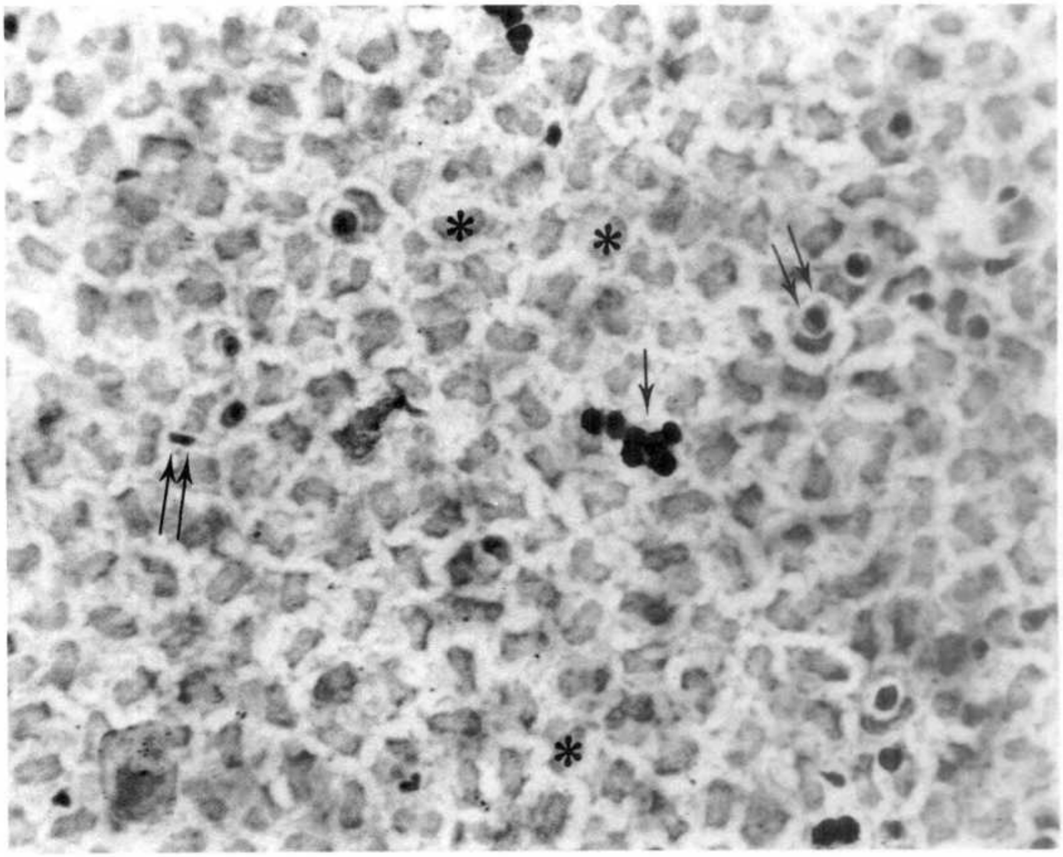


Figure 8 Immunoperoxidase stained and hematoxylin counterstained flat mount of the corneal endothelium of an HSV-1 infected rabbit taken 19 days after infection. The endothelial layer contained both immunoperoxidase-positive plasma cells (arrow) and immunoperoxidase-negative infiltrating cells (nuclei stained with haematoxylin, double arrows) and endothelial cells (asterisks.) (Original magnification ×400.)

chronic HSV disease, while a few significant morphometric changes were observed in the endothelium of another patient.[23]

Our data provide evidence to support a mechanism by which HSV induces corneal oedema without virus destruction of endothelial cells. The data show the development and recovery from corneal oedema without measurable loss of endothelial cells or major changes in morphometric parameters. The isolate of HSV-1 (RE) used in these studies as well as the HF and Walker strains of HSV-1 have been shown to be unable to disseminate within the cornea. These strains of virus, however, induce corneal oedema.[11 15 24] The inflammatory disease induced by HSV-1 may result not from loss of corneal endothelial cells but rather from loss of cell function. It is not clear whether barrier or 'pump' function or both may be altered owing to HSV infection. Decompensation of corneal endothelial function due to infiltration with inflammatory and immune cells may be responsible for the oedema. The presence of these cells suggests that chemotactic factors as well as inflammatory mediators and cytokines are present in the cornea. Metabolites of arachidonic acid which contribute to inflammation have been shown to be produced within the cornea during HSV-1 infection.[25] Further studies will be required to determine the identity of cytokines and mediators of inflammation present in HSV infected corneas in order to determine their role in corneal oedema.

The research presented here was supported by grants EY-07120 and EY-01931 from the National Institutes of Health, Bethesda, MD, and by an unrestricted grant from Research to Prevent Blindness, Inc, New York, NY.

1 Pavan-Langston D. Viral diseases: Herpetic infections. In: Smolin G, Throft RA, eds. *The cornea Scientific foundations and clinical practice*. Boston: Little, Brown, 1987: 240–67.

2 Wander AH, Centifanto YM, Kaufman HE. Strain specificity of clinical isolates of herpes simplex virus. *Arch Ophthalmol* 1988; **98:** 1458–61.

3 Hyndiuk RA, Glaser DD. Herpes simplex keratitis. In: Tabbara K, Hyndiuk RA, eds. *Infections of the Eye*. Boston: Little, Brown, 1986; 343–68.

4 Vannas A, Ahonen R, Makitie J. Corneal endothelium in herpetic keratouveitis. *Arch Ophthalmol* 1983; **101:** 913–5.

5 Nesburn AB. Immunological aspects of ocular herpes simplex disease. In: Suran A, Gery I, Nussenblatt RB. *Immunology of the eye*. Washington, DC: IRL Press, 1980: 21–42.

6 Sundmacher R. Clinical aspects of herpetic eye diseases. *Curr Eye Res* 1987; **6:** 183–8.

7 Sundmacher R. A clinico-virologic classification of herpetic anterior segment diseases with special reference to intraocular herpes. In: Sundmacher R, ed. *Herpetische Augenerkrankungen*. Munich: Bergmann, 1981: 203–10.

8 Vannas A, Ahonen R. Herpetic endothelial keratitis. A case report. *Acta Ophthalmol (Kbh)* 1981; **59:** 296–301.

9 Ahonen R, Makitie J. Herpes simplex virus anterior uveitis. In: Saari KM, ed. *Uveitis update*. Amsterdam: Elsevier, 1984: 157–62.

10 Oh JO. Endothelial lesions of rabbit cornea produced by herpes simplex virus. *Invest Ophthalmol Vis Sci* 1970; **9:** 196–205.

11 Maloney ED, Kaufman HE. Dissemination of corneal herpes simplex. *Invest Ophthalmol Vis Sci* 1965; **4:** 872–5.

12 Cook SD, Brown SM. Herpes simplex virus type 1 persistence and latency in cultured rabbit corneal epithelial cells, keratocytes and endothelial cells. *Br J Ophthalmol* 1986; **70:** 642–50.

13 Carter C, Dyson H, Easty DL. Herpes simplex virus infection of corneal cells in vitro. In: Maudgal PC, Missotten L, eds. *Herpetic eye diseases*. Dordrecht: Junk, 1985: 9–14.

14 Irvine AR, Kimura SJ. Experimental stromal herpes simplex keratitis in rabbits. *Trans Am Ophthalmol Soc* 1967; **65:** 189–210.

15 Meyers-Elliott RH, Chitjian PA, Billups CL. Effect of cyclosporine A on the corneal inflammatory response in herpes simplex virus keratitis. *Exp Eye Res* 1987; **45:** 281–303.

16 McNeill JI, Kaufman HE. Local antivirals in a herpes simplex stromal keratitis model *Arch Ophthalmol* 1979; 97: 727–9.

17 Metcalf JF, Kaufman HE. Herpetic stromal keratitis – evidence for cell-mediated immunopathogenesis. *Am J Ophthalmol* 1976; 82: 827–34.

18 Yee RW, Geroski DH, Matsuda M, Champeau EJ, Meyer LA, Edelhauser HF Correlation of corneal endothelial pump site density, barrier function and morphology in wound repair. *Invest Ophthalmol Vis Sci* 1985, 26: 1191–201

19 Taylor MJ, Hunt CJ Dual staining of corneal endothelium with trypan blue and alizarin red S. importance of pH for the dye-lake reaction. *Br J Ophthalmol* 1981, 65: 815–9

20 Geroski DH, Edelhauser HF. Morphometric analysis of the corneal endothelium Specular miscroscopy vs alizarin red staining. *Invest Ophthalmol Vis Sci* 1989; 30: 254–9.

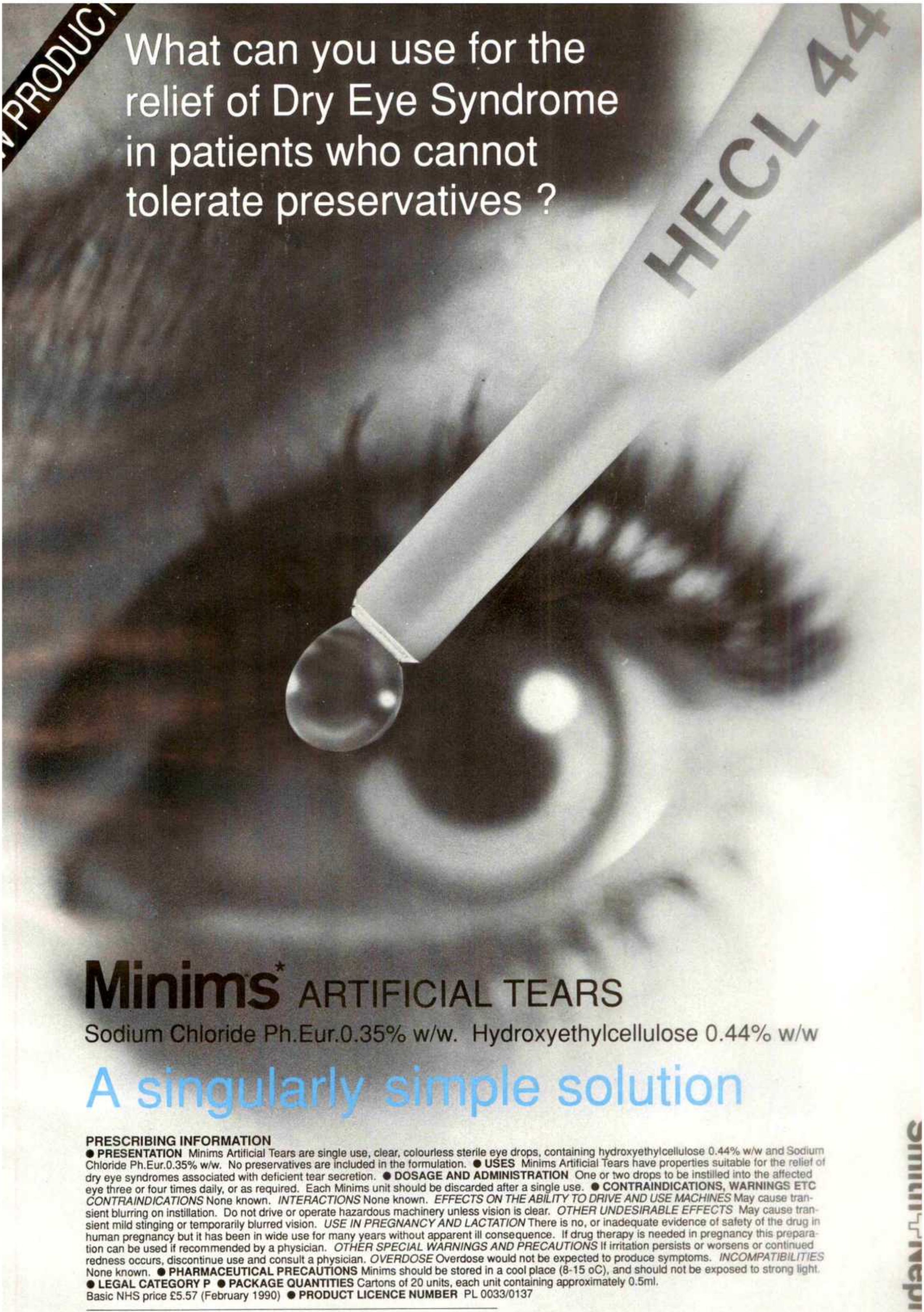
21 Shimeld C, Lewkowicz-Moss SJ, Lipworth KM, Hill TJ, Blyth WA, Easty DL. Antigens of herpes simplex virus in whole corneal epithelial sheets from mice. *Arch Ophthalmol* 1986; 104: 1830–4.

22 Edelhauser HF, Van Horn DL, Miller P, Pederson HJ Effect of thiol-oxidation of glutathione with diamide on corneal endothelial function, junctional complexes, and microfilaments. *J Cell Biol* 1976; 68: 567–78

23 Ikebe H, Takamatsu T, Itoi M, Fujita S. Changes in nuclear DNA content and cell size of injured human corneal endothelium *Exp Eye Res* 1988, 47: 205–15

24 Edelhauser HF, Schultz RO, Van Horn DL. Experimental herpes simplex keratitis: corneal hydration, electrolyte content and structural changes *Am J Ophthalmol* 1969, 68: 458–66

25 Birkle DL, Sanitato JJ, Kaufman HE, Bazan NG Arachidonic acid metabolism to eicosanoids in herpes virus-infected rabbit cornea. *Invest Ophthalmol Vis Sci* 1986, 27: 1443–6.



What can you use for the relief of Dry Eye Syndrome in patients who cannot tolerate preservatives ?

Minims* ARTIFICIAL TEARS

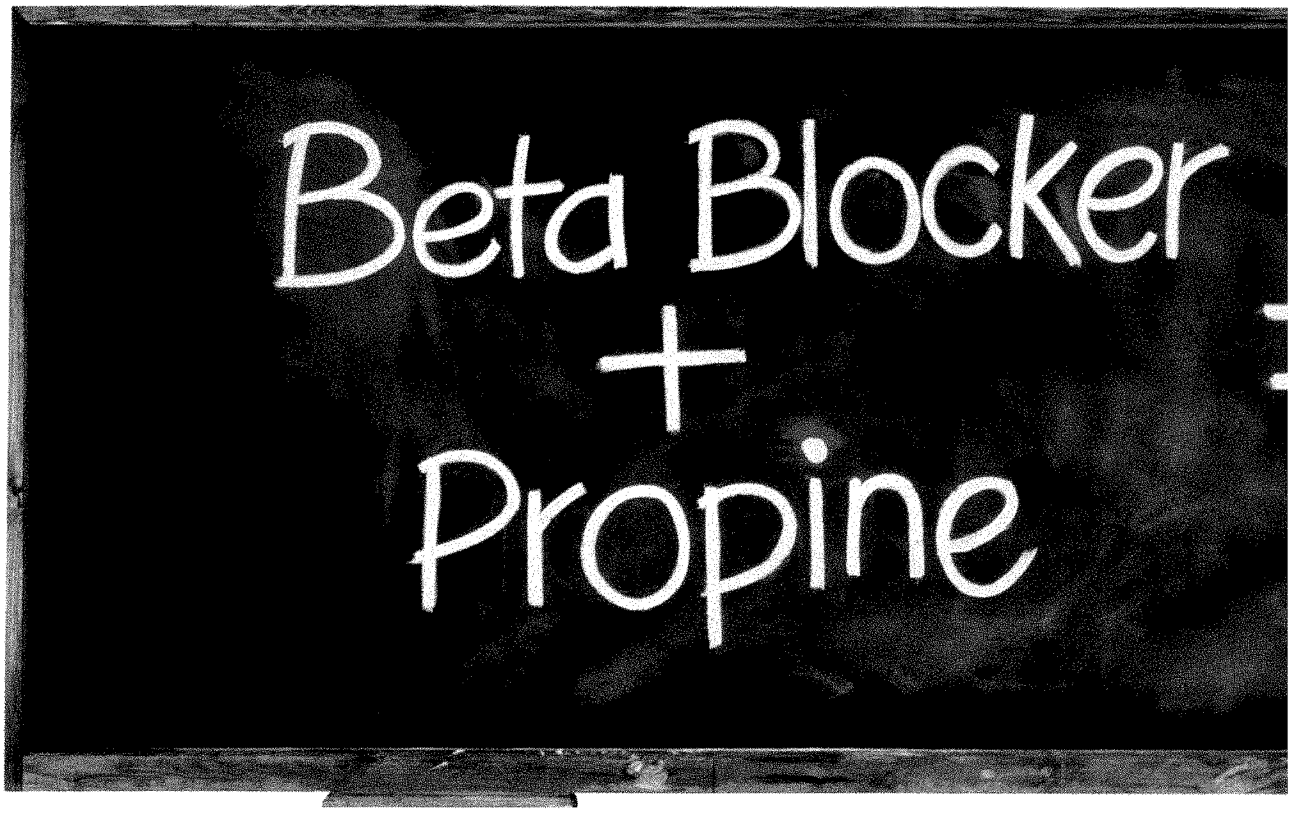
Sodium Chloride Ph.Eur.0.35% w/w. Hydroxyethylcellulose 0.44% w/w

A singularly simple solution

PRESCRIBING INFORMATION
● **PRESENTATION** Minims Artificial Tears are single use, clear, colourless sterile eye drops, containing hydroxyethylcellulose 0.44% w/w and Sodium Chloride Ph.Eur.0.35% w/w. No preservatives are included in the formulation. ● **USES** Minims Artificial Tears have properties suitable for the relief of dry eye syndromes associated with deficient tear secretion. ● **DOSAGE AND ADMINISTRATION** One or two drops to be instilled into the affected eye three or four times daily, or as required. Each Minims unit should be discarded after a single use. ● **CONTRAINDICATIONS, WARNINGS ETC** *CONTRAINDICATIONS* None known. *INTERACTIONS* None known. *EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES* May cause transient blurring on instillation. Do not drive or operate hazardous machinery unless vision is clear. *OTHER UNDESIRABLE EFFECTS* May cause transient mild stinging or temporarily blurred vision. *USE IN PREGNANCY AND LACTATION* There is no, or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence. If drug therapy is needed in pregnancy this preparation can be used if recommended by a physician. *OTHER SPECIAL WARNINGS AND PRECAUTIONS* If irritation persists or worsens or continued redness occurs, discontinue use and consult a physician. *OVERDOSE* Overdose would not be expected to produce symptoms. *INCOMPATIBILITIES* None known. ● **PHARMACEUTICAL PRECAUTIONS** Minims should be stored in a cool place (8-15 oC), and should not be exposed to strong light. ● **LEGAL CATEGORY P** ● **PACKAGE QUANTITIES** Cartons of 20 units, each unit containing approximately 0.5ml.
Basic NHS price £5.57 (February 1990) ● **PRODUCT LICENCE NUMBER** PL 0033/0137

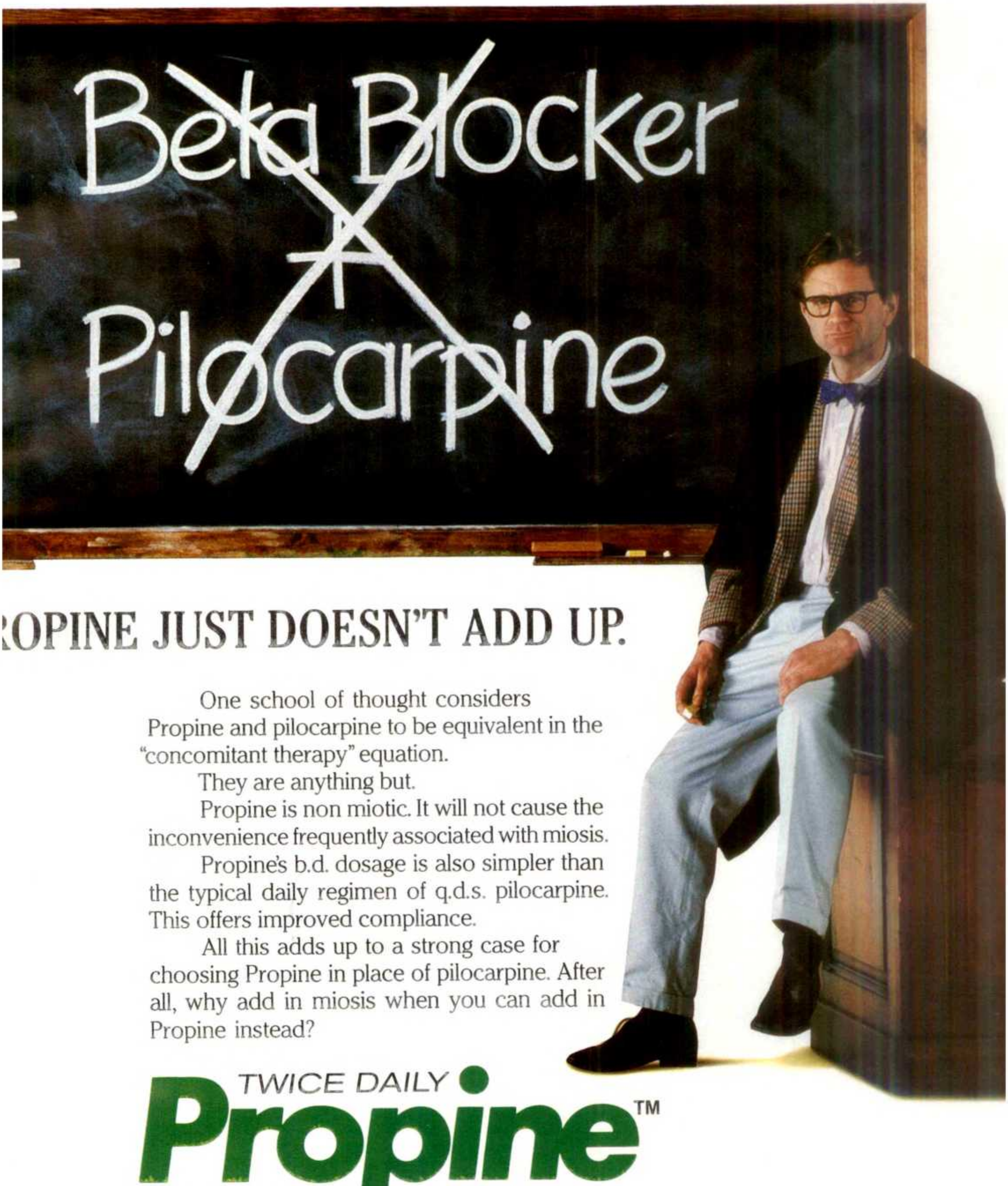
Smith & Nephew Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, Essex RM3 8SL
Tel: (04023) 49333. Telex: 898058 SMINEPG. Fax: (04023) 71316

* Trade Mark



EQUATING PILOCARPINE WI

PROPINE™ Prescribing Information
Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin
during pregnancy has not been substantiated. *Precautions:* Dipivefrin should b
with caution in patients with narrow angles since dilation of the pupil may trig
attack of angle closure glaucoma. Macular oedema is a rare occurrence with adre
use in aphakic patients. Prompt reversal generally follows discontinuance of th
Macular oedema with dipivefrin does present as a possibility in the aphakic patien
product contains benzalkonium chloride and should not be used by patients cont
to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachy
arrhythmias and hypertension have been reported with ocular administrati



OPINE JUST DOESN'T ADD UP.

One school of thought considers Propine and pilocarpine to be equivalent in the "concomitant therapy" equation.

They are anything but.

Propine is non miotic. It will not cause the inconvenience frequently associated with miosis.

Propine's b.d. dosage is also simpler than the typical daily regimen of q.d.s. pilocarpine. This offers improved compliance.

All this adds up to a strong case for choosing Propine in place of pilocarpine. After all, why add in miosis when you can add in Propine instead?

TWICE DAILY

Propine™

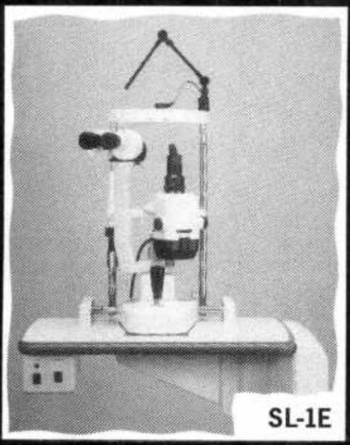
dipivefrin hydrochloride

A CLEAR CHOICE IN THE GLAUCOMA EQUATION

enaline, and may occur rarely with Propine therapy. Ocular: the most frequently
rted side-effects are conjunctival injection, and burning and stinging on instillation.
ound vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis,
e been reported occasionally. Adrenochrome deposits in the conjunctiva and cornea
e been associated rarely with use of dipivefrin. Follicular conjunctivitis has been
orted during long term therapy with Propine. The condition is reversible upon discon-
ance of the drug. **Pharmaceutical precautions** Store at room temperature. Discard
unused contents 28 days after opening the bottle. **Legal category** POM. **Package quantities** Plastic dropper bottle containing 10 ml. **Further information** The active ingredient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Product licence number** 0426/0040. **Basic NHS cost:** (as at February 1990) £4.89. **Date of preparation** February 1990.

TM denotes trademark

ALLERGAN PHARMACEUTICALS

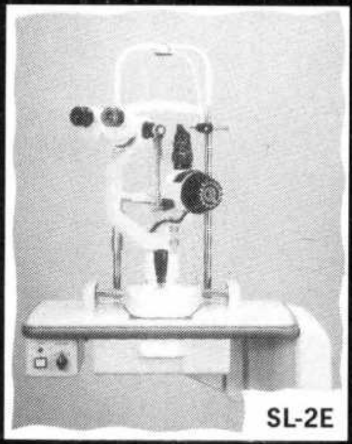


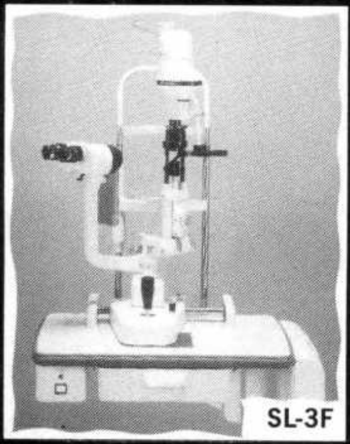
SL-1E

- 0-14mm continuous slit width
- 1-14mm stepped slit length
- Variable magnification
- 3 built in filters
- Halogen illumination
- Omni directional joystick

SL-2E

- 0-12mm continuous slit width
- 1-12mm continuous slit length
- 3 built in filters
- Variable magnification
- Halogen illumination
- Omni directional joystick
- Optional
  Observation tube
  35mm camera set



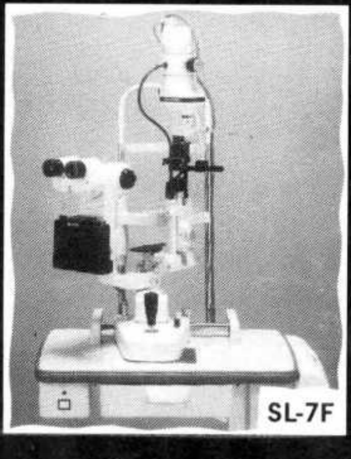


SL-3F

- 0-10mm continuous slit width
- 1-10mm continuous slit length
- Variable magnification
- 0-20 degree stepped slit inclination
- 4 built in filters
- Halogen illumination
- Omni directional joystick

SL-7F

- 0-9mm continuous slit width
- 1-8mm continuous slit length
- Variable magnification
- 0-20 degrees stepped slit inclination
- 4 built in filters
- Halogen illumination
- Omni directional joystick
- Multi-coated Optics
- Optional
  Observation tube
  35mm camera set
  Video attachment



A full range of Slit Lamps from Keeler – exclusive UK distributors of TOPCON equipment.

This extensive range of high quality instruments allows you to choose a Slit Lamp that fully meets your individual requirements.

The introduction of the NEW SL-3F and SL-7F Slit Lamps (replacing the SL-3E and SL-6E) enhances the range.

Whilst maintaining the integrity of the original design, these new high precision Slit Lamps are ergonomically designed to incorporate:

- Smoother positioning
- Finer control
- An accessible brightness control
- Improved Optics

With the new modern colour and design these Slit Lamps are sure to enhance your practice.

For more detail and literature, please contact Keeler Ltd.

TOPCON

Keeler

KEELER LTD
Clewer Hill Road, Windsor, Berkshire SL4 4AA
Telephone: (0753) 857177
Telex: 847565/846588 Fax: (0753) 857817

LONDON CENTRE AT
John Bell and Croyden, 50-54 Wigmore Street,
London W1H 0AU
Telephone: 071-935 8512

SCOTLAND CENTRE
25 Deerdykes View, Westfield Estate,
Cumbernauld G68 9HN
Telephone: (0236) 721214 Fax: (0236) 721231

British Journal of Ophthalmology, 1990, 74, 731–733

Objective autorefraction in posterior chamber pseudophakia

Palaniswamy Sunder Raj, Tayo Akingbehin, Anthony M Levy

Abstract

Automated refraction with the Canon RK-1 Autoref keratometer was evaluated in 110 eyes (110 patients) six to eight weeks after they had undergone extracapsular cataract extraction with posterior chamber intraocular lens implantation and achieved a best corrected visual acuity of at least 6/12. Autorefraction readings were obtained in 100 (91%) of these eyes. The agreement between autorefraction and clinical refraction data was 98% for spherical equivalence <0·51 dioptres (D), 95% for sphere power <0·51D, 94% for cylinder power <0·51D, and 85% for cylinder axis <11°. Autorefraction can provide acceptably accurate postoperative refraction values in pseudophakic eyes.

Autorefractors (AR) are being increasingly used in busy ophthalmology clinics because they can be operated by a nurse or technician,[1] are much quicker than manual refraction,[1 2] and are readily accepted by most patients.[1] Recent experience indicates that objective autorefraction provides reliable and valid preliminary refraction data,[1-12] especially in subjects who cannot accommodate owing to aphakia[2 13] or cycloplegia.[1 2 14 15]

Intraocular lenses (IOL) can interfere with the accuracy of objective ARs[1 9 10 16] by scattering the measuring infrared beam and increasing 'noise'.[10 16] Attempts have been made to overcome this problem in modern ARs by providing an 'IOL setting' which can be switched on to improve the signal-to-noise ratio in the recording system while refracting pseudophakes. We evaluated the use of one such instrument, the Canon RK-1 Autoref keratometer, in patients with posterior chamber IOLs prior to its introduction into routine clinical use.

Patients and methods

INSTRUMENT

The Canon RK-1 Autoref keratometer combines both automated refraction and keratometry in one instrument (Fig 1). In the autorefraction mode infrared rays are projected on to the patient's retina and the reflected illumination is detected by an array of photodetectors. This is based on the Scheiner double pinhole principle, which enables the AR to determine the ocular refraction in three meridians. The instrument then computes and displays the objective ocular refraction in terms of sphere, cylinder, and axis corrected for a vertex distance of 12 mm.

The AR covers a pupillary area of 2·9 mm and can measure up to 15 dioptre (D) sphere, 7 D cylinder, and axis between 1° and 180° in increments of 0·12 D or 1°. It has an in-built autofogging mechanism consisting of a phototarget which is supposed to relax completely the patients' accommodation. An IOL setting is present which can be switched on to improve the accuracy of refraction in pseudophakes.

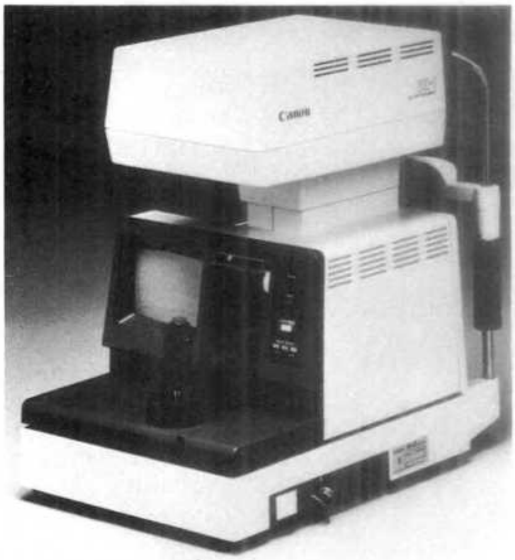


Figure 1 The Canon RK-1 Autoref keratometer.

The measurement of refraction is made in 0·05 second, which is facilitated by sensor assisted alignment and focusing over a built-in television monitor. The iris of the eye to be measured is clearly focused, the ring target is aligned with the pupil, and the measurement button pressed to display the objective ocular refraction. Any number of such measurements may be performed either in the single or continuous mode. The refractive data displayed can be printed out if necessary. If more than three measurements have been performed the computer automatically calculates and prints the most reliable or 'standard' values from the last three to five data.

Low reliability of the measurement due to movement of the eye during testing, postoperative deformation of the cornea or iris, and eccentricity of the IOL are indicated by a special 'reliability mark' (henceforth referred to as 'less reliable' data). Improper alignment, droopy eyelashes or eyelids, and insufficient pupillary size require appropriate remedial action when the signal error is displayed on the television monitor, as valid readings cannot otherwise be obtained. More detailed operating and maintenance information is available in the accompanying instrument manual.

PATIENTS AND EYES

This was a prospective study carried out between

Department of Ophthalmology, District General Hospital, Southport PR8 6NJ
P Sunder Raj
T Akingbehin
A M Levy

Correspondence to:
T Akingbehin FRCS.

Accepted for publication 21 June 1990

six and eight weeks following extracapsular cataract extraction with the implantation of a posterior chamber IOL. When both the eyes of a patient fulfilled the above criteria, only the right eye was studied. Of the 129 such patients seen consecutively in the eye clinic 19 were excluded because their studied eyes did not attain a best corrected visual acuity of at least 6/12. Valid AR values could not be obtained for various reasons in 10 patients, leaving 100 eyes of 100 patients which were analysed.

METHODS

All the refractions, both clinical as well as on the autorefractor, were carried out by the same examiner (PSR) without the use of either mydriatics or cycloplegics. Objective clinical refraction (streak retinoscopy) was first carried out, followed by subjective verification to achieve the best possible visual acuity. Autorefraction was then performed, and a series of three readings were obtained from each eye. The 'standard' refractive value in the AR printout data (categorised into reliable and less reliable data) was then compared with the final prescription based on clinical refraction for degree of agreement.

STATISTICAL ANALYSIS

The statistical significance of the difference between the less reliable (indicated by the reliability mark) and reliable autorefractive data was evaluated by (1) χ^2 test on the number of eyes (patients) in the two groups within 0·51 D of spherical equivalence, spherical power, or cylindrical power and within 11° in cylindrical axis as determined by clinical refraction; and (2) standard error of the difference between means on the mean difference in the various refractive components between automated and conventional refraction.

Table 1 Degree of agreement between autorefractive and clinical refractive data of various refractive components

	Autorefractor reading; no (%)		
Refractive component	*Reliable (n=70)*	*Less reliable (n=30)*	*Total (n=100)*
Spherical equivalent			
±0·25 D	57 (81%)	19 (63%)	76
±0·50 D	70 (100%)	28 (93%)	98
±1·00 D	70 (100%)	30 (100%)	100
Sphere component			
±0·25 D	56 (80%)	18 (60%)	74
±0·50 D	70 (100%)	25 (83%)	95
±1·00 D	70 (100%)	30 (100%)	100
Cylinder component			
±0·25 D	53 (76%)	18 (60%)	71
±0·50 D	70 (100%)	24 (80%)	94
±1·00 D	70 (100%)	29 (99%)	99
Cylinder axis			
±5°	33 (47%)	10 (33%)	43
±10°	63 (90%)	22 (73%)	85
≥11°	3 (4%)	5 (17%)	8
*NC	4 (6%)	3 (10%)	7

n=Number of eyes (patients).
*No cylinder in one of the methods of refraction

Table 2 Mean difference and standard deviations (SD) between autorefraction and clinical refraction

	Autorefractor reading, mean (SD)*		
Refractive component	*Reliable (n=70)*	*Less reliable (n=30)*	*Total (n=100)*
Spherical equivalent (D)	−0·01 (0·11)	−0·02 (0·37)	−0·01 (0·29)
Sphere component (D)	−0·03 (0·23)	−0·08 (0·46)	−0·04 (0·45)
Cylinder component (D)	0·09 (0·40)	0·15 (0·45)	0·12 (0·40)
Cylinder axis (degrees)	4·1 (3·2)	6·1 (5·4)	4·7 (6·1)

n=Number of eyes (patients).
*The minus (−) sign indicates more myopia or less hypermetropia on the autorefractor than by clinical refraction

Results

For the 110 eyes (110 patients) with posterior chamber IOLs which were eligible for the study valid autorefractive data could not be obtained in 10 eyes (10 patients). Various reasons included cylinder values outside the range of the instrument (five patients), inability to keep the eyes focused on the target (two patients), uncontrolled blinking, head tremor, and confusion (one patient each). Further analysis of the eyes whose cylinder values could not be estimated by the AR revealed that on clinical refraction the cylinder values in dioptres ('plus') were 5·0, 5·5, 6·25, 6·5, and 7·25.

The percentage agreement between autorefraction and clinical refractive data with respect to the various refractive components is depicted in Table 1. More than 90% of the autorefraction values were within 0·51 D of spherical equivalence, sphere, and cylinder powers. This figure rose to nearly 100% when only reliable readings on the AR were considered. 85% of the cylindrical axis values determined by the AR were within 11° of clinical refraction, improving to 90% with reliable measurements alone. The percentage agreement between the AR and clinical refractive data in the reliable and less reliable autorefractive data groups was compared by the χ^2 test. This revealed that there was a statistically significant difference between the above two AR groups in spherical equivalence ($p<0{\cdot}05$), sphere power ($p<0{\cdot}005$), cylinder power ($p<0{\cdot}001$), and cylinder axis ($p<0{\cdot}05$).

In seven eyes a cylinder value was present in one of the two methods of refraction (that is, either on the AR or during clinical refraction) but not in the other. Aurorefraction indicated a cylinder value in six of these eyes (three in the reliable group and three in the less reliable group) where none was found on clinical testing. A single eye needed cylindrical correction during subjective verification, but this was not displayed by the AR.

The mean differences between autorefraction and clinical refraction in spherical equivalence, sphere power, cylinder component, and cylinder axis are shown in Table 2. Spherical equivalence and sphere component were both more myopic or less hypermetropic on the AR in comparison with conventional refraction, unlike the cylinder power, which was more hypermetropic and less myopic. The mean difference in cylinder axis was 4·7° (SD 6·1°).

Autorefractive data were categorised into reliable and less reliable values. The differences between mean reliable AR values and clinical refraction data were computed and compared with values derived in a similar fashion for less reliable data. Tested by the standard error of the difference between the means to assess statistical significance, the two groups showed no difference in spherical equivalence ($p>0\cdot9$), sphere power ($p>0\cdot7$), or cylinder power ($p>0\cdot6$). However, the mean difference in cylinder axis was significant ($p<0\cdot0001$).

Discussion

Extracapsular cataract extraction followed by posterior chamber IOL implantation is the current method of choice in the visual rehabilitation of cataract patients. With preoperative ocular biometry the surgeon can achieve the desired postoperative refraction in a significant number of patients.[17] However, ocular refraction will continue to play an important part in the postoperative evaluation and visual rehabilitation of pseudophakic eyes until bifocal or multifocal IOLs achieve their promised potential.

An autorefractometer which can be operated by the nursing staff to provide accurate refraction values in pseudophakes will result in an appreciable saving of the clinician's time. Previous reports on autorefraction in pseudophakic eyes have not been adequately comprehensive. Rassow and Wesemann[1] classified results as good, bad, or instrument failure in terms of the visual acuity achieved with the autorefractor reading compared with subjective refraction. Wood[10] found that IOLs accounted for a significant number of unobtainable or rejected AR measurements. Dufier *et al*[2] studied a general clinic population which included normal, aphakic, and pseudophakic eyes, but pseudophakes were not separately analysed.

In this study the various autorefractive data in pseudophakic eyes were all acceptably accurate, especially as preliminary refraction. Subjective verification of this result is essential before final prescription. A similar outcome with the AR has been experienced in normal patients[14] and children[15] under cycloplegia. In comparison, manifest autorefraction in normal subjects has yielded poorer results for spherical equivalence, with percentage agreement with clinical refraction being as low as 41%.[12] This is probably because the in-built autofogging mechanism in the AR fails to neutralise adequately the patient's accommodation, producing significant instrument myopia.[14 15] This phenomenon does not affect aphakes or pseudophakes who lack accommodation, accounting for autorefraction results which are superior to those observed in subjects with intact accommodation.[1 2 4–10 12 14]

Although differential analysis of the reliable and less reliable AR reading showed a statistically significant difference between the two groups, this was not clinically important,[14] as the autorefractive data were considered as preliminary results needing subjective verification.

It is not only the accuracy of the autorefraction measurements that is important but also the percentage of a given number of eyes that can be measured with an AR. AR readings were either invalid or not obtainable in 9% (10 out of 110) of the eyes eligible for study where conventional refraction was possible. This is lower than the 25%[10] and 60%[4] mentioned in previous studies on autorefraction which have included pseudophakic eyes.

Five eligible eyes (5%) could not be measured by the AR because the cylinder values were supposedly outside its specified range. On subjective refraction all but one eye had a cylinder power of less than +7 D. Possibly the patients with these eyes had difficulty in accepting subjectively the high powered cylindrical correction, and hence the cylindrical power determined clinically was less than that indicated objectively by autorefraction. It is also possible that the AR tended to overestimate the cylinder component, as this was skewed towards more plus or less minus in comparison with clinical refractive data. The routine clinical practice in our unit is to adjust or remove corneal sutures after eight weeks if there is a cylindrical correction greater than 2·5 D. The five eyes mentioned above had their corneal sutures removed, but subsequent AR values have not been included in this study.

Six of the study eyes which had a cylinder component on the AR did not need it on subjective verification. Ghose *et al*,[7] in their study of autorefraction in normal subjects, have pointed out that cylinder values obtained on the AR were often clinically insignificant.

The clinical impression gained during this evaluation was that autorefraction was both quick and easy to perform. Although this procedure was not timed and compared with conventional refraction, a saving in the clinician's time of four minutes per eye has been reported in a clinic setting.[2]

In conclusion, it is suggested that an AR with a special facility for refracting pseudophakic eyes has a useful role to play in the routine evaluation of pseudophakes, particularly if these values are treated as preliminary refraction data requiring subjective verification.

We wish to thank Sister Anne Lewis for administrative help and Miss Lisa Jones for secretarial assistance.

1 Rassow B, Wesemann W. Automatic infra-red refractors. *Ophthalmology* 1984; 91(S). 10–26.
2 Dufier JL, Abitbol M, Pigamo F, Prete T, Paris JP, Poitreuand O. Automatic objective refractometer: evaluation in 3618 eyes. *J Fr Ophtalmol* 1987, 10: 301–8.
3 Guyton DL. Automated refractors – 1983 *Ophthalmology* 1983; 90(9S): 36–44.
4 French CN, Wood ICJ. The Dioptron in practice *Optician* 1981; 181: 18–30.
5 Wong EK, Patella V, Pratt M, Myers S, Gaster R, Irving HL Clinical evaluation of the Humphrey automatic refractor. *Arch Ophthalmol* 1984; 102: 870–5.
6 Wood ICJ, Papas E, Burghardt D, Hardwick G. A clinical evaluation of the Nidek autorefractor *Ophthalmic Physiol Opt* 1984; 4: 169–78.
7 Ghose S, Nayak BK, Singh JP. Critical evaluation of the NR-1000F autorefractometer. *Br J Ophthalmol* 1986; 70: 221–6.
8 Reddy NS, Agarwal S. Clinical evaluation of the Topcon autorefractor. *Indian J Ophthalmol* 1987; 35: 407–10
9 Wesemann W, Rassow B. Automatic infra-red refractors – a comparative study. *Am J Optom Physiol Opt* 1987, 64: 627–38.
10 Wood ICJ. A review of autorefractors. *Eye* 1987; 1: 529–35.
11 Anonymous. Refractors *Ophthalmology* 1988; 95(S): 171–6.
12 Ehrlich DL. The Canon RK-1: refractor mode evaluation. *Ophthalmic Physiol Opt* (in press).
13 Guillon M. Automated refraction in aphakia-II. Its repeatability and accuracy compared to conventional techniques *Ophthalmic Physiol Opt* 1986; 6: 85–9.
14 Nayak BK, Ghose S, Singh JP A comparison of cycloplegic and manifest refractions on the NR-1000F (an objective autorefractometer). *Br J Ophthalmol* 1987; 71: 73–5.
15 Hunold W, Auffarth G, Effert R. Clinical application of the Canon R-10 autorefractor in children with squint. *Klin Monatsbl Augenheilkd* 1988; 192: 58–65
16 Charman WN Infra-red autorefractors – here to stay? *Ophthalmic Physiol Opt* 1985, 5: 237–9
17 Dang MS, Sunder Raj PP. SRK II formula in the calculation of intraocular lens power. *Br J Ophthalmol* 1989; 73: 823–6

British Journal of Ophthalmology, 1990, **74**, 734–738

Randomised single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery

C D G Jenkins, P J McDonnell, D J Spalton

Abstract

Comparatively little attention has been paid to the conjunctival toxicity of antibiotics administered at the time of cataract surgery. We have observed the effect of subconjunctival gentamicin and cefuroxime injection, using colour photography in a randomised single blind trial of 121 patients undergoing routine cataract surgery. Our results suggest that a hyperaemic eye is likely to occur about twice as often in patients injected with gentamicin ($p<0{\cdot}001$). Gentamicin is associated with more pain postoperatively ($p<0{\cdot}05$). Significant manifestations of gentamicin toxicity are conjunctival oedema and capillary closure. Cefuroxime has some theoretical advantages over gentamicin in its antibacterial spectrum.

The rational use of antimicrobial prophylaxis for any surgical procedure requires that the risk of infection is high and that the effects of infection are severe.[1] Most of the studies of the incidence of endophthalmitis following cataract surgery were performed over two decades ago; even then its incidence was low, being of the order of 1·30%.[2] The use of antibiotic prophylaxis can therefore be justified only on account of the poor visual outcome of intraocular infection. The low incidence of infection has necessitated that clinical trials on the prophylactic use of antibiotics in cataract surgery be performed over many years, with vast numbers of patients, in which it is almost impossible to keep other variables constant, such as advances in surgical technique. Reported therapeutic regimens have varied widely, not only in the choice of antibiotic but also in the route and timing of administration in relation to surgery. As a consequence no completely satisfactory prospective clinical trials have ever been performed.

Department of Ophthalmology, St Thomas's Hospital, London SE1 7EH
C D G Jenkins
P J McDonnell
D J Spalton

Correspondence to:
Mr D J Spalton, Medical Eye Unit, St Thomas's Hospital, Lambeth Palace Road, London SE1 7EH.

Accepted for publication 21 June 1990

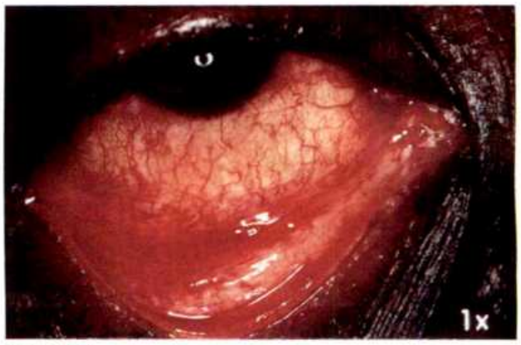


Figure 1B

There is, however, reasonable circumstantial evidence that prophylactic antibiotics in some form lower the risk of postoperative endophthalmitis. Thus, Allen and Mangiaracine[3] reported an incidence of 0·75% in 660 patients operated on without prophylactic antibiotics. In 26 307 patients treated preoperatively with chloramphenicol eyedrops the incidence of endophthalmitis fell by a factor of 35 to 0·022%.[4] There have been no comparatively large trials of endophthalmitis in patients given subconjunctival prophylaxis. Perhaps the best is that of Kolker *et al*,[5] who reported an incidence of 1·42% in 494 patients given no prophylaxis compared with 0·21% in 480 patients given subconjunctival penicillin and streptomycin. In a further series of 1480 patients given subconjunctival antibiotics (penicillin and streptomycin in the absence of a history of sensitivity to these drugs) they reported an incidence of 0·14%, a 10-fold decrease. Interestingly these were caused by organisms resistant to the antibiotics injected at the time of surgery. Pearlman[6] compared an unspecified regimen of topical antibiotics to a combination of subconjunctival penicillin and streptomycin. Nine cases of endophthalmitis occurred in 1773 cataract operations given topical prophylaxis compared with three in 3226 cases given subconjunctival penicillin and streptomycin. By contrast Christy and Lall,[8] in a

Figure 1 Typical appearances 24 hours postoperatively of minimal conjunctival reaction (1A), conjunctival hyperaemia (1B), and conjunctival oedema (1C).

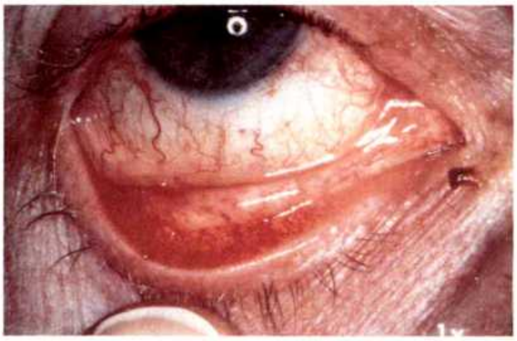


Figure 1A

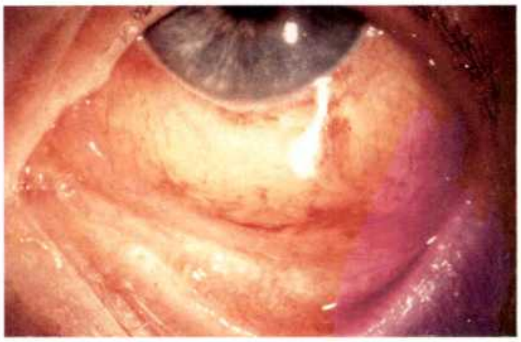


Figure 1C

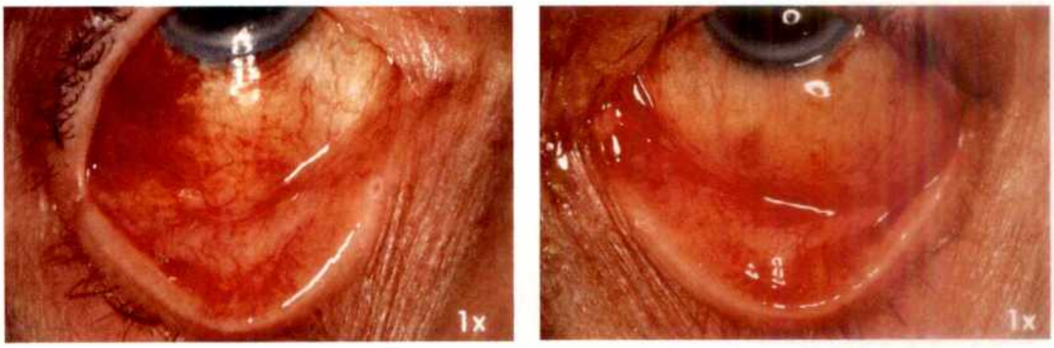


Figure 2A *Figure 2B*

Figure 2 This patient received cefuroxime to the right eye (2A) and gentamicin to the left eye (2B) after bilateral sequential cataract surgery. Although there is some subconjunctival haemorrhage in the right eye, the vasculature is normal, whereas in the left eye there is vascular closure and conjunctival oedema.

large relatively uncontrolled trial of 54 261 patients in India and Pakistan, did not find any superiority with the subconjunctival route of administration. In their control group of 3798 patients receiving topical antibiotics only 0·45% developed endophthalmitis. The incidence of endophthalmitis following subconjunctival injection varied from 0·37% in 2514 patients given 500 000 units penicillin, to 0·56% in 4112 patients given 100 mg chloramphenicol and 0·76% in 1709 patients given 10 mg or 20 mg gentamicin.

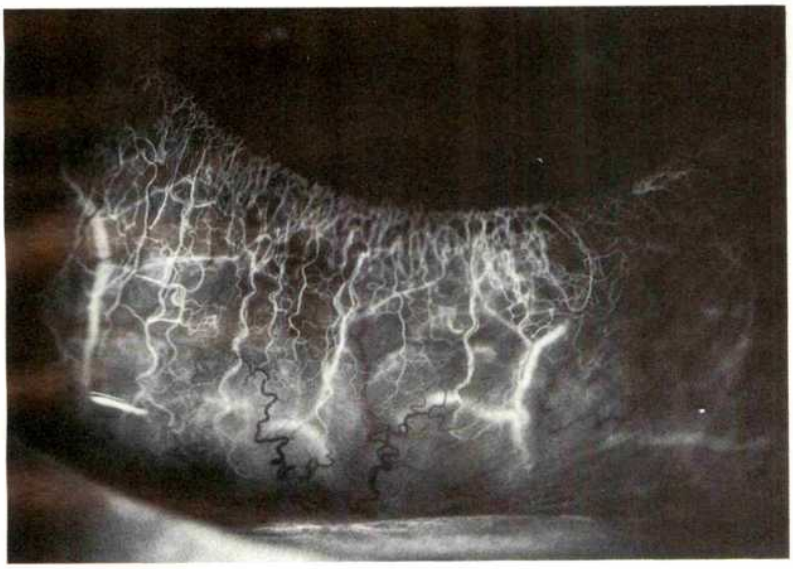


Figure 3A(a)

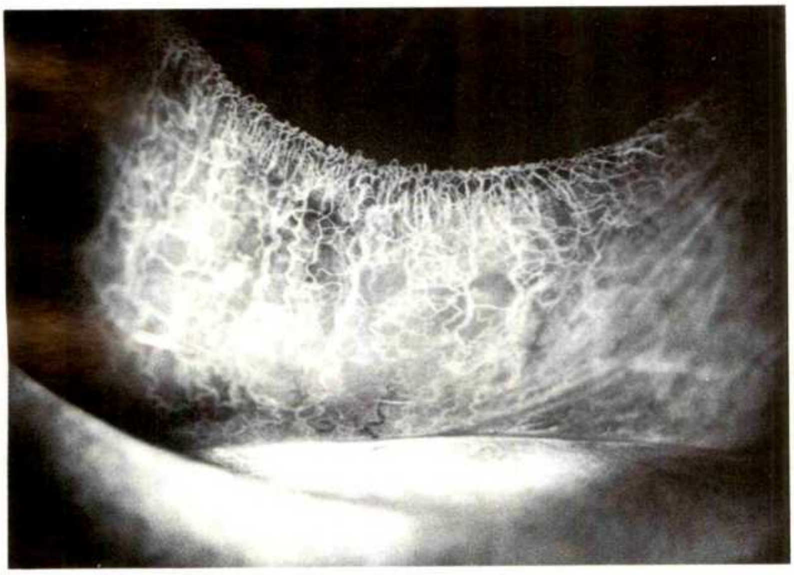


Figure 3A(b)

Figure 3 Fluorescein angiograms of three eyes 24 hours postoperatively. 3A (cefuroxime): (a) patchy filling 18 seconds after fluorescein injection; (b) the vessels have filled at 22 seconds and show a normal vascular pattern. 3B (gentamicin): (a) patchy filling after 19 seconds with (b) some vessels remaining unfilled at 25 seconds. 3C (gentamicin): (a) marked vascular closure at 14 seconds, (b) persisting at 29 seconds.

It is therefore widely accepted that prophylactic antibiotics in some form lower the incidence of endophthalmitis, and this is largely reflected in current ophthalmological practice. In a recent survey of prominent American cataract surgeons gentamicin administered subconjunctivally proved to be the most popular form of prophylaxis.[9]

In principle the choice of antibiotic is governed by the bacterial flora likely to cause endophthalmitis and the antibiotic's spectrum, intraocular penetration, and local toxicity. The question of conjunctival toxicity and patient tolerance has been relatively underexplored in the published literature.[10] This study was therefore undertaken to compare the postoperative effects on the conjunctiva of gentamicin or cefuroxime given subconjunctivally at routine uncomplicated cataract and implant surgery.

Material and methods

We performed a prospective study of patients undergoing extracapsular and posterior chamber implant surgery at St Thomas's Hospital between November 1988 and November 1989. One hundred and twenty eight consecutive patients were randomised to receive either gentamicin or cefuroxime. All received topical chloramphenicol for 24 hours prior to surgery, which was performed under local or general anaesthetic by one of four experienced surgeons. At the end of the procedure the antibiotic was injected under the inferior bulbar conjunctiva. Either 125 mg cefuroxime (Glaxo) was administered in 1 ml of water, or 20 mg gentamicin (Rousell) was administered in a volume of 0·5 ml. Twenty four hours after surgery colour photographs were taken of the inferior bulbar conjunctiva with a Nikon Medical Eye camera at ×1 magnification.

At the conclusion of the study the photographs were scrambled, and two of the surgeons were

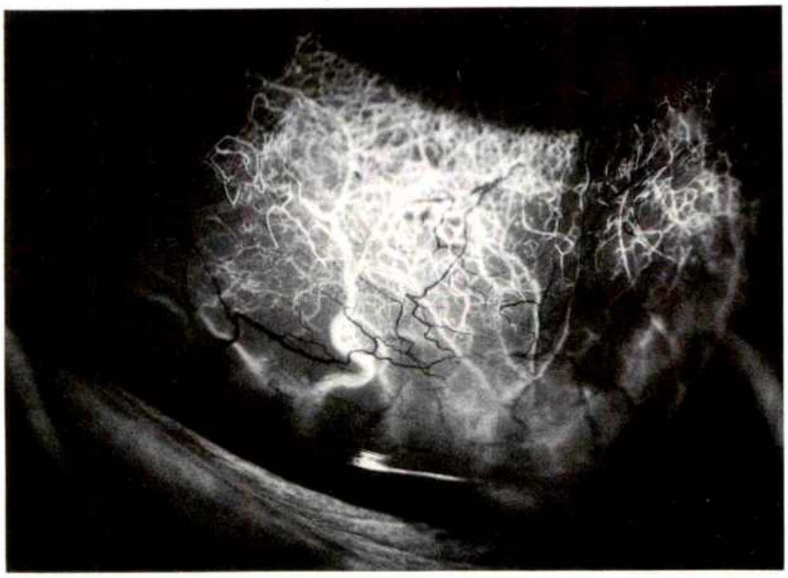


Figure 3B(a)

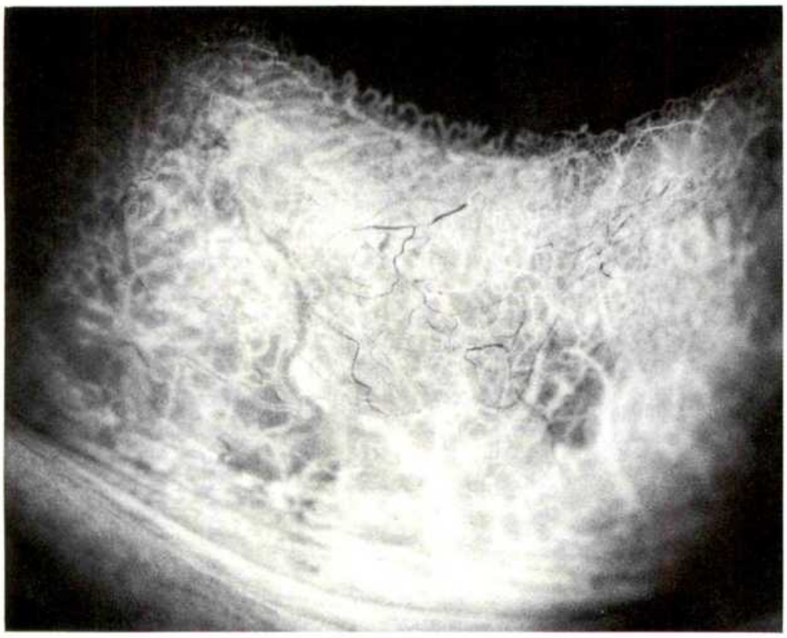


Figure 3B(b)

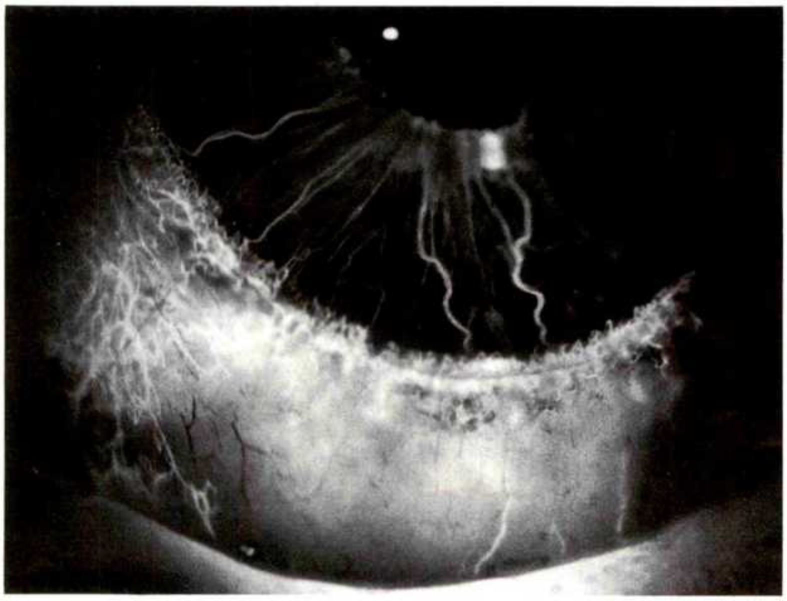


Figure 3C(a)

asked to separate them on a forced choice basis into two not necessarily equal groups, according to the degree of conjunctival reaction. Eyes with subconjunctival haemorrhage of sufficient density to make interpretation impossible were excluded. This was repeated two weeks later in order to assess intraobserver variability. Eyes with marked conjunctival oedema and haemorrhage were then analysed separately.

Forty three patients were asked to categorise the amount of ocular discomfort they had experienced in the 24 hours following their operation in one of the following groups: no discomfort, very mild discomfort, mild discomfort, moderate discomfort, quite painful, and very painful. These assessments were graded from 0 to 5 accordingly. In six patients fluorescein angiography of the site of subconjunctival injection was performed according to the method described by Meyer and Watson.[11]

Results

Figs 1A, 1B, and 1C are representative of the slides presented to the two observers and show a white, hyperaemic, and oedematous postoperative conjunctival appearance respectively. Figs 2A and 2B are the photographs of a patient who had bilateral cataract extractions performed by the same surgeon, with cefuroxime being administered to the right eye (Fig 2A) and gentamicin to the left eye (Fig 2B). One of the major differences between the two slides is the oedema in the eye which received gentamicin, which as shown in Table 4, is significantly associated with subconjunctival gentamicin. Figs 3A, 3B, and 3C are examples of angiography of the conjunctiva and episclera 24 hours after antibiotic injection, and demonstrate the vascular closure and leakage associated with subconjunctival gentamicin.

Seven patients were excluded from the main part of the study because excessive subconjunctival haemorrhage precluded assessment of other conjunctival changes. Five of these patients had been given cefuroxime and two gentamicin. Conjunctival changes were therefore compared in the remaining 121 patients, and the results for each observer are shown in Tables 1 and 2. These show that eyes injected with gentamicin were twice as likely to be hyperaemic as those injected with cefuroxime.

Intra- and interobserver variability was assessed by the κ statistic, since this corrects for the amount of agreement that might be expected from chance alone. It ranges between $+1$ (complete agreement) to -1 (complete disagreement). Figures greater than 0·7–0·75 are considered to signify good agreement. Results for intraobserver variability (Tables 1 and 2) show good individual agreement over time for both observers ($\kappa=0·7$). The interobserver results (Table 3) suggest that there were differences in the way that the photographs were being assessed – or, put another way, differences in the interpretation of conjunctival reaction – by the two surgeons. We therefore ascertained whether certain specific features such as oedema and subconjunctival haemorrhage were associated with the antibiotic injected. Table 4 shows that

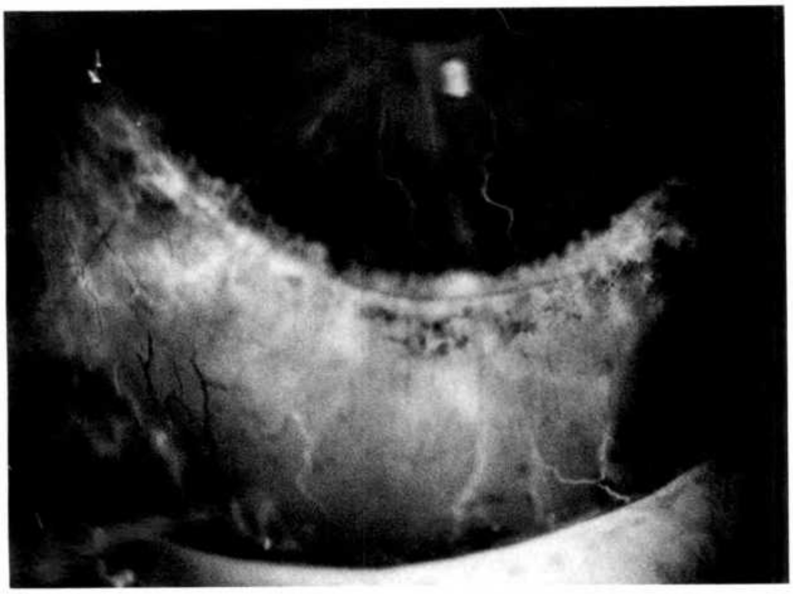


Figure 3C(b)

conjunctival oedema was more common after gentamicin injection (p<0·001). There was a significant difference in the way that patients with conjunctival oedema were graded (p<0·01), and this probably accounts for the difference in scoring between the two observers (Table 3). Table 5 shows that, although subconjunctival haemorrhage is more common after gentamicin, this was of no statistical significance, and there was little difference between the observers in the scoring of this sign (p<0·5). It is probable, therefore, that subconjunctival haemorrhage results directly from injection. In Fig 4 the response of 43 patients to pain is illustrated. These results suggest that gentamicin is associated with more postoperative discomfort than is cefuroxime (p<0·05).

Discussion

Our results suggest that, at the doses used, subconjunctival cefuroxime injection at the time of cataract surgery causes less conjunctival toxicity, less discomfort, and leaves a whiter eye

Table 1 Correlation between subconjunctival antibiotic and inflammation as scored by observer 1

	First scoring – observer 1			*Second scoring – observer 1*		
	Gentamicin	*Cefuroxime*	*Total*	*Gentamicin*	*Cefuroxime*	*Total*
Inflamed	44	18	62	41	17	58
White	17	42	61	20	43	63
Total	61	60	121	61	60	121
	$\chi^2=21{\cdot}47$ (p<0·001)			$\chi^2=18{\cdot}32$ (p<0·001)		

Variability between two scorings: $\kappa=0{\cdot}7$.

Table 2 Correlation between subconjunctival antibiotic and inflammation as scored by observer 1

	First scoring – observer 2			*Second scoring – observer 2*		
	Gentamicin	*Cefuroxime*	*Total*	*Gentamicin*	*Cefuroxime*	*Total*
Inflamed	32	18	50	35	20	55
White	29	42	71	26	40	66
Total	61	60	121	61	60	121
	$\chi^2=6{\cdot}29$ (p<0·02)			$\chi^2=7{\cdot}05$ (p<0·01)		

Variability between two scorings: $\kappa=0{\cdot}7$.

Table 3 Interobserver variability

Observers	κ
Observer 1 (first scoring) vs observer 2 (first scoring)	0·30
Observer 1 (first scoring) vs observer2 (second scoring)	0·50
Observer 1 (second scoring) vs observer 2 (first scoring)	0·38
Observer 1 (second scoring) vs observer 2 (second scoring)	0·49

Table 4 Correlation of conjunctival oedema with antibiotic

Oedema	*Gentamicin*	*Cefuroxime*	*Total*
Yes	26	7	33
No	35	53	88
Total	61	60	121

$\chi^2=14{\cdot}61$ (p<0·001).

Table 5 Correlation of subconjunctival haemorrhage with antibiotic

Haemorrhage	*Gentamicin*	*Cefuroxime*	*Total*
Yes	21	12	33
No	42	53	95
Total	63	65	128

$\chi^2=2{\cdot}74$ (p<0·1).

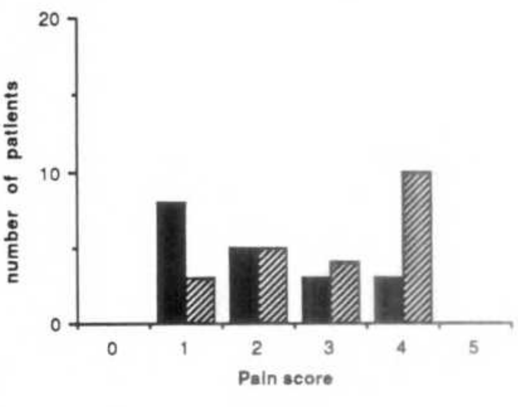
Table 6 Aetiology of endophthalmitis

(a) Pseudophakic endophthalmitis, diagnosis and management: Driebe et al.[12] *83 cases of endophthalmitis in pseudophakic eyes 75% culture-positive (n=63)*		*(b) Infectious endophthalmitis; review of 36 cases: Puliafito* et al.[11] *Recent postoperative cases following cataract extraction (n=17)*	
Staph. epidermidis	38%	*Staph epidermidis*	58%
Staph. aureus	21%	*Staph aureus*	12%
Streptococcus spp	11%	Diptheroids	6%
Proteus spp	6%	*Proteus mirabilis*	6%
Propionobacterium	5%	*Pseudomonas*	6%
Pseudomonas	3%	*Serratia*	6%
Others (8)	16%	*Cephalosporium*	6%

Table 7 Comparison of in-vitro sensitivities to cefuroxime and gentamicin of organisms commonly cultured in postoperative endophthalmitis[14-16]

	MIC-90 (mg/l)	
	Cefuroxime	*Gentamicin*
Staph epidermidis	8·0	22·63
Staph aureus	0·25	0·12–1·0
Str. pyogenes	<0·125	16
Str. pneumoniae	<0·125	16–32
Proteus mirabilis	2·2	2·0–8·0
Pseudomonas	>125	1·0–8·0
Proprionobacterium	(0·1–0·2)*	25–50

*MIC (minimum inhibitory concentration) for cefoxitin.



Z = 2.18 (p<0.05)

Figure 4 Postoperative pain experienced by patients injected with cefuroxime ■ and gentamicin ▨. Pain was graded by the patients from 0 (no discomfort) to 5 (severe pain).

than does gentamicin. Although one of the major aims of ocular surgery is to minimise trauma to the eye, the problem of conjunctival toxicity is not by itself enough to change established surgical practice. Clearly the choice of antibiotic in cataract surgery must be determined both by its spectrum against the organisms most commonly implicated in endophthalmitis, and by its intraocular penetration. Two large recent series of cases of endophthalmitis following cataract surgery were reported by Driebe *et al*[12] and Puliafito *et al*[13] and their findings are summarised in Table 6. The published sensitivities[14-16] of cefuroxime and gentamicin to these organisms are shown in Table 7 and illustrate that, with the important exception of pseudomonas, the mean inhibitory concentrations are generally better for cefuroxime than for gentamicin.

Aqueous penetration of these antibiotics is an equally important consideration. Although aqueous concentrations following subconjunctival cefuroxime have not been published, other cephalosporins achieve much higher aqueous concentrations than gentamicin at conventional doses. Thus the mean aqueous concentration following 20 mg subconjunctival gentamicin is 6·7 μg/ml (mg/l) (when administered 30 minutes before surgery)[17] compared with 120 mg following 125 mg ceftazidime (when administered at a mean of 107 minutes before surgery).[18] It is apparent, therefore, that subconjunctival gentamicin would be a poor choice with which to treat endophthalmitis caused by *Staphylococcus epidermidis* and streptococci, which between them account for over 16 times as many cases as pseudomonas. Note also that propionobacterium, an organism recently shown to be implicated in chronic indolent cases of endophthalmitis or so-called lens induced uveitis, is much more sensitive to cephalosporins than to gentamicin. The combination of superior spectrum and intraocular penetration indicates that cefuroxime is the more logical choice with which to prevent postoperative endophthalmitis, though this assertion has not been demonstrated clinically.

The cause of the greater conjunctival toxicity of gentamicin is unknown, but could be related either to the way the drug is administered or to a factor intrinsic to the molecule itself. In this study gentamicin was administered in a smaller volume (0·5 ml) than was cefuroxime (1 ml); thus it is unlikely that the volume of administration is important. It may, however, be related to its administration in a solution of low osmolarity (180 mosm/l), compared with that of cefuroxime (505 mosm/l). Equally, pH could be an important factor, since gentamicin is much more acidic (pH 4·5) than is cefuroxime (pH 6·3). Fluorescein angiography (Fig 3) shows that gentamicin causes both capillary closure and leakage, and this may be related to the clinical conjunctival changes.

This study has clearly demonstrated the superiority of cefuroxime to gentamicin in terms of conjunctival toxicity and patient tolerance, and there are theoretical advantages in its spectrum and ocular penetration. We therefore recommend the use of cefuroxime rather than gentamicin for the prevention of endophthalmitis following intraocular surgery.

We thank S Lim for his assistance with the colour photography and S Ford at the Western Ophthalmic Hospital for her expertise in fluorescein angiography.

1 Jackson GG. Considerations of antibiotic prophylaxis in nonsurgical high risk patients. *Am J Med* 1981; **70:** 467–73.
2 Starr MB. Prophylactic antibiotics for ophthalmic surgery. *Surv Ophthalmol* 1983; **27:** 353–73.
3 Allen HF, Mangiaracine AB. Bacterial endophthalmitis after cataract extraction. *Arch Ophthalmol* 1964; **72:** 455–62.
4 Allen HF, Mangiaracine AB. Bacterial endophthalmitis after cataract extraction. II. Incidence in 36 000 consecutive operations with special reference to preoperative antibiotics. *Arch Ophthalmol* 1974; **91:** 3–7.
5 Kolker AE, Freeman MI, Pettit TH. Prophylactic antibiotics and postoperative endophthalmitis. *Am J Ophthalmol* 1967; **63:** 434–9.
6 Pearlman MD. Prophylactic subconjunctival penicillin and streptomycin after cataract extraction. *Arch Ophthalmol* 1956; **55:** 516–8.
7 Cassady JR. Prophylactic subconjunctival antibiotics following cataract extraction. *Am J Ophthalmol* 1967; **64:** 7–12.
8 Shepard DD. Consultation section. *J Cataract Refract Surg* 1987; **13:** 682–7.
9 Goulstine DB, Marmion VJ. Subconjunctival gentamicin. *Br J Ophthalmol* 1971; **55:** 478–80.
10 Meyer PAR, Watson PG. Low dose fluorescein angiography of the conjunctiva and episclera. *Br J Ophthalmol* 1987; **71:** 2–10.
11 Driebe WT, Mandelbaum S, Forster R, Schwartz L, Culbertson W. Pseudophakic endophthalmitis. *Ophthalmology* 1986; **93:** 442–8.
12 Puliafito CA, Baker AS, Haaf J, Foster CS. Infectious endophthalmitis: review of 36 cases. *Ophthalmology* 1982; **89:** 921–9.
13 Kucers A, Bennett N. *The use of antibiotics.* 3rd ed. London: Heinemann, 1979: 267–93, 325–58.
14 Eykyn S, Jenkins C, King A, Philipps I. Antibacterial activity of cefuroxime, a new cephalosporin antibiotic, compared with that of cephaloridin, cephalothin, and cefamandole. *Antimicrob Agents Chemother* 1976; ??: 690–5.
15 Wang WLL, Everett ED, Johnson M, Dean E. Susceptibility of Propionobacterium acnes to seventeen antibiotics. *Antimicrob Agents Chemother* 1977; **11:** 171–3.
16 Matholone MBR, Harden A. Penetration and systemic absorbtion of gentamicin after subconjunctival injection. *Br J Ophthalmol* 1972; **56:** 609–12.
17 Clements DB, Tailor V. A study of aqueous and serum levels of ceftazidime following subconjunctival injection. *Br J Ophthalmol* 1987; **71:** 433–5.

Which is the natural tear and which is Tears Naturale™?

Tears Naturale ophthalmic solution was developed exclusively for dry eye treatment, alleviating dry spots associated with both aqueous and mucin deficiencies.

This close similarity to the action of natural tears is made possible by the unique Duasorb™ polymer system contained in Tears Naturale.

The Duasorb polymer system mimics the action of conjunctival mucin by increasing wettability of the ocular surface and stabilising the tear film.

The low viscosity and high retention time of Tears Naturale helps to ensure patient comfort, patient satisfaction and, therefore, patient compliance.

Tears Naturale: so near to tears.

Send for full details to:

TEARS NATURALE™

Dextran 70 + Hydroxypropyl Methylcellulose

Alcon
Dedicated to Excellence
Alcon Laboratories (UK) Ltd
Imperial Way Watford Herts WD2 4YR
Telephone: 0923 246133
Fax: 0923 243331

TM denotes trademark of Alcon Laboratories

Presentation: Dextran 70 0.1% and Hydroxypropyl Methylcellulose 0.3% in a sterile solution preserved with Benzalkonium Chloride BP 0.01% and Disodium Edetate BP 0.05%. **Clincal Uses:** A soothing solution for use as an artificial tear and lubricant in the relief of dry eye syndromes associated with deficient tear secretion or deficient mucous. **Dosage and Administration:** Instill 1 or 2 drops into the eye(s), as frequently as to relieve eye irritation symptoms. **Contra-indications:** The product contains Benzalkonium Chloride, and should not be used when soft contact lenses are being worn. **Precautions:** If irritation persists, discontinue use. **Product Licence No:** 0649/0031.

UNIVERSITY OF LONDON

INSTITUTE OF OPHTHALMOLOGY

Associated with MOORFIELDS EYE HOSPITAL

Please note the correction of dates below for the

Lasers in Ophthalmology Course

20th-22nd March 1991

Dean's Office,
Institute of Ophthalmology,
17-25 Cayton Street,
London EC1V 9AT
Phone: 071 387 9621

**CLINICAL NEURO-OPHTHALMOLOGY COURSE
AT THE
INSTITUTE OF NEUROLOGICAL SCIENCES
THE BEAUMONT HOSPITAL**

MONDAY MAY 27th – FRIDAY MAY 31st 1991

This course covers clinical neuro-ophthalmology with emphasis on clinical demonstration. In addition all aspects of relevant basic science are covered in the lecture programme.

COURSE ORGANISERS:

Professor Peter Eustace
Ms. P. Logan
Mr. T. Buchanan

COURSE FEE:

IR £150

APPLICATIONS TO:

**Ms. Anne Carter,
Department of Ophthalmology,
University College Dublin,
Mater Misericordiae Hospital,
Eccles Street,
Dublin 7, IRELAND**

Combined—VITREORETINAL SURGERY—MEDICAL RETINA COURSE

SARASOTA, FLORIDA • FEBRUARY 7 - 9, 1991

Topics To Be Covered:

- Viscodissection Techniques in PDR
- When & How to use TPA
- Photocoagulation for Diabetic Macular Edema, Grid vs Focal
- PDR Photocoagulation in Difficult Cases
- Intraoperative use of Heavier-Than-Water Fluids
- Surgery of the Vitreous Base
- Use of Intraocular Gases vs Silicone Oil
- Case Selection & Algorithm for Success in Pneumatic Retinopexy
- Surgery for Impending Macular Holes
- Management of IOFB's
- Instrumentation Update
- Surgical Management of ROP
- Macular Pucker
- Endophthalmitis Medical vs Surgical Treatment
- Laser Treatment for Complications of CRVO and BRVO
- Treatment of CNVM An Update from the MPS
- Medical & Surgical Evaluation of the Uveitis Patient
- When is Laser Photocoagulation Indicated for Lattice &/Or Retinal Breaks Without Detachment
- Retinal Dystrophy Update
- Diabetic Retinopathy & Pregnancy
- Complications of Fluorescein Angiography
- Management of Subfoveal & Recurrent Choroidal Neovascularization
- Complications of Laser Treatment

Credits:

14 Hours in Category 1, AMA
University of South Florida

Registration:

- $450.00 Ophthalmologists
- $150.00 Residents & Fellows

Faculty:

- *Mark Blumenkranz, M.D.*
- *Charles Garcia, M.D.*
- *Bert Glaser, M.D.*
- *Ronald G. Michels, M.D.*
- *Robert Murphy, M.D.*
- *David Orth, M.D.*
- *Paul Sternberg, M.D.*
- *Lawrence Singerman, M.D.*

COURSE CO-DIRECTORS:

- *Miguel A. Arcacha, Jr., M.D.*
- *W. Sanderson Grizzard, M.D.*

Information:

CALL OR WRITE
Lauri Fagan
ASSOCIATED RETINAL SURGEONS
1700 S Tuttle Avenue, Suite 3
Sarasota, Florida 34239
(813) 952-0900

British Journal of Ophthalmology, 1990, 74, 739–742

Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function

Michael F Marmor

Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA 94305, USA
M F Marmor

Correspondence to Michael F Marmor, MD

Accepted for publication 5 July 1990

Abstract

Thioridazine toxicity has been described as a 'progressive chorioretinopathy', but this designation can be misleading. During the first year after thioridazine exposure retinal pigmentation evolves from a granular to a patchy or nummular appearance. However, visual function and the electroretinogram typically improve during this period. Some cases may show chorioretinal atrophy and functional loss many years later, but there is little evidence for ongoing drug-related progression. Late atrophy may represent degeneration of cells that were injured subclinically at the time of initial drug exposure. Although thioridazine toxicity produces an evolving pigmentary disturbance, functional changes must be monitored independently of fundus appearance.

Toxicity from thioridazine has been recognised since 1960.[1] Ingestion of high doses (typically exceeding 800 mg/day) for just a few weeks may be sufficient to cause symptoms of reduced acuity and poor dark adaptation.[1-5] If retinopathy is recognised at this early stage, the fundus characteristically shows coarse granular pigmentation involving the macula and sometimes mid periphery as well. However, these granular changes evolve over time into large, patchy areas of hypo- or hyperpigmentation.[2,3] This change in appearance has been recognised for a long time, but recent articles have attached new significance to the findings: the late appearance has been termed a 'nummular retinopathy',[6] and the evolution of pigmentation called 'progressive chorioretinopathy'.[7]

The latter terminology implies that thioridazine toxicity progresses after the drug has been stopped, as has been reported occasionally with chloroquine toxicity.[8-11] However, clinical experience with thioridazine is not altogether consistent with this description. For example, functional recovery within the first several months after stopping the drug has been noted repeatedly.[4,12,13] It is critical to make distinctions between short and long term changes, between the evolution of pigmentation and the evolution of functional loss, and between pharmacological toxicity (from retained toxin) and the time related decompensation of subclinically injured tissue.

Material and methods

We have seen seven cases of thioridazine toxicity for whom broad retinal functional parameters (electroretinogram, dark adaptation or visual fields) were measured sequentially. In four cases the examinations included the first year after toxic exposure; in six cases the examinations extended to between 5½ and 28 years after exposure. Table 1 summarises the drug history, fundus changes and visual function studies of these patients.

Table 1 Case histories and clinical findings

		Length of					*Extent of*			
Case	*Sex*	*Dose (mg/day)*	*Exposure (at high dose)*	*Time after exposure*	*Age*	*Fundus appearance*	*Visual acuity (best eye)*	*Visual field (perimetry)*	*Dark adaptation (log units threshold elevation)*	*Scotopic ERG* (% of normal min amplitude)*
1	M	2400	5 Weeks	0	38	—	20/70	—	—	—
				3 Weeks	38	Granular	20/30	3°	—	—
				2 Months	38	—	20/30	4°	—	—
				3 Months	38	—	20/25	3°	—	—
				5 Months	38	Pigm coalesced	20/25	22°	—	—
				13 Months	39	Clumps, nummular	20/25	20°	2	5
2	F	1800	4–6 Weeks	2 Months	25	Granular	20/100	20°	4	0*
				1 Year	26	Nummular	20/25	Scotomas	0·75	Normal
				2 Years	27	Nummular	20/30	Scotomas	—	—
				5½ Years	31	Nummular	20/30	Normal	—	Normal
3	F	900–1200	2–3 Years	0	29	Granular	20/60	3°	—	0*
				7 Years	36	Nummular	20/25	10°	2	5–10
				11 Years	40	Nummular	20/50	10°	—	—
				15½ Years	45	Nummular	20/30	5°	—	—
4	M	1600	2 Months	1 Month	27	Granular	20/25	—	0·3	Normal
				15 Years	41	Mild nummular	20/20	Scotomas	Normal	Normal
5	M	1200	>5 Weeks	16 Years	48	Nummular	20/25	Scotomas	2	50
			(3–4 Years	17 Years	49	Nummular	[20/80]	[5°]	2	50
			on drugs)	18½ Years	51	Nummular	20/25	Scotomas	2	50
6	F	?	1 Year	4 Years	35	Nummular	20/20	—	—	—
				14 Years	45	Nummular	20/20	Scotomas	1	50
				20 Years	52	Nummular	20/25	Scotomas	2	45
7	M	2400	Few months	0	28	—	Reduced	—	—	—
				2 Months	28	—	20/30	—	—	—
				13 Years	41	Nummular	20/40	15°	2 5	25
				28 Years	56	Atrophic	20/25	2°	3·5	0

*Hand held flash recordings; all others made with full field stimulus

Figure 1 Fundus appearance of case 3. (A) Soon after stopping thioridazine: granular retinopathy. (B) Seven years later: patchy nummular retinopathy. (C) Eleven years after thioridazine: there has been enlargement of some of the demarcated atrophic zones (arrows) that lie within larger areas of RPE damage.

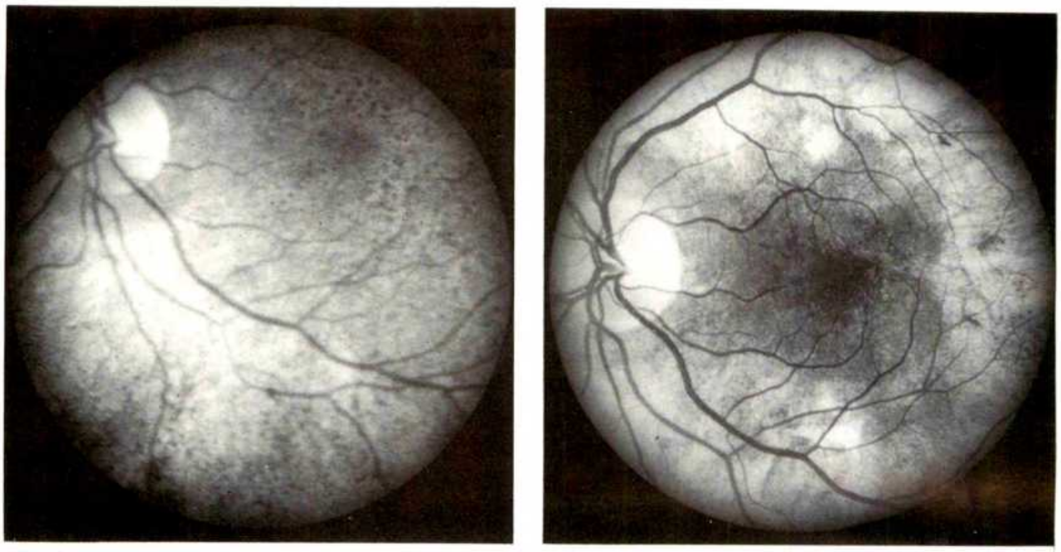


Fig 1A *Fig 1B*

Results

Figs 1–2 illustrate the typical progression of fundus changes. Soon after stopping thioridazine the fundus had a coarse granular appearance, most striking in the posterior pole (Fig 1A). Over the first year after cessation of the drug the pigment coalesced to produce larger pigment clumps and areas of geographic atrophy or nummular retinopathy (Fig 1B). Over the ensuing years the atrophic zones tended to enlarge very slowly, though the basic pattern of atrophy was remarkably constant over long periods of time (Fig 1C). Occasionally the nummular retinopathy progressed to diffuse end-stage atrophy (Figs 2A, B).

The functional changes associated with the early evolution (granular to nummular) and late evolution (nummular expansion) of thioridazine retinopathy are quite different. During the first year after exposure to the drug visual function typically improved despite the evolution of pigmentary changes in the fundus. Fig 3 illustrates the early functional status of cases 1–4 by the best available sequential data – electroretinogram (ERG), dark adaptation, or visual field. Visual function was often depressed during the first few months of the toxic exposure, but showed a degree of recovery thereafter. Once the fundus appearance had stabilised (roughly one year after drug exposure), visual function either remained stable (Fig 4) or showed a rate of deterioration that was extremely slow and was measurable only over a period of several years. Fig 5 illustrates the late functional status of cases 2–7.

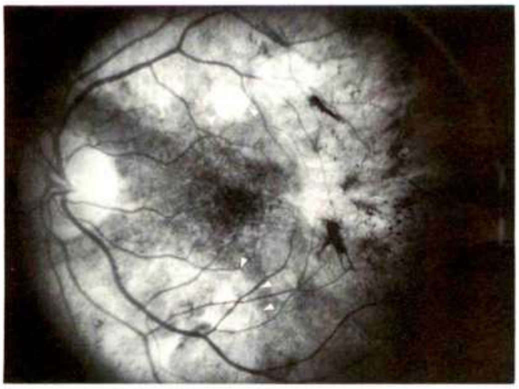


Fig 1C

Case 5 seemed for a while to contradict this description, insofar as he complained of a rapid loss of visual acuity and visual field that began 16 years after stopping thioridazine. During the course of one year he progressed from good peripheral vision with isolated scotomas to severe tunnel vision with only a tiny 5° central island, and he sought training in the use of a long cane. However, his nummular fundus lesions changed only minimally during this period, and his ERG remained stable. Confronted with the inconsistencies, he miraculously 'recovered'.

Discussion

The fundus appearance in thioridazine retinopathy evolves within the first year from the coarse granular retinopathy of acute toxicity to the patchy or nummular retinopathy of late thioridazine damage (Fig 1). However, all our cases showed significant visual improvement (or at worst, stability), during the first year after toxic levels of thioridazine were stopped, despite an increasingly atrophic fundus appearance. For example, patient 2, who initially had a very low ERG (extinguished to a hand held flash) recovered to show almost normal responses. These observations are consistent with reports of visual recovery when the drug is stopped before retinal damage is too pervasive.[4,12,13] Thus it appears that thioridazine retinopathy does not progress functionally during the change from granular to nummular retinopathy.

Improvement during the first year after thioridazine does not rule out the possibility that the drug might continue to exert a toxic effect over the long term if drug depots remain in the tissues. Thioridazine (like other phenothiazines) is bound to melanin and may well persist in the eye for a long time.[14,15] Our data show that there is a risk of very slow or very late functional decompensation, and cases of late functional loss have also been reported by others,[3,7] including two that were decumented with ERGs.[6,16] At the same time the relative stability of findings in some of my patients suggests that late functional loss may not be inevitable.

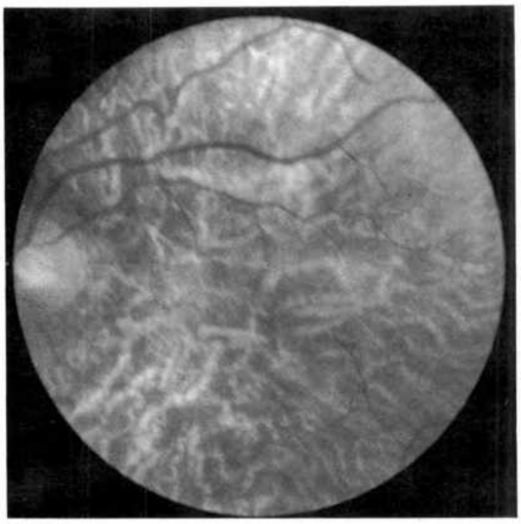


Fig 2A

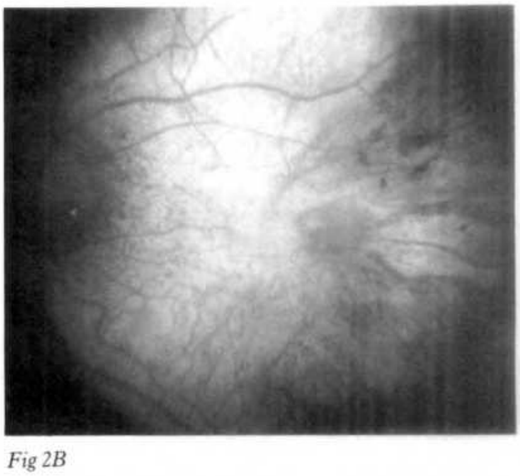


Fig 2B

Figure 2 Fundus appearance of case 7. (A) Thirteen years after stopping thioridazine: patchy and diffuse RPE atrophy. (B) Twenty eight years after thioridazine: end-stage chorioretinal atrophy.

It seems clear from our experience and published reports[6,7] that the geographic areas of chorioretinal atrophy in thioridazine toxicity may expand very slowly. But do these late degenerative changes represent a direct pharmacological effect of thioridazine in the tissues? I find it difficult to believe that enough drug would persist to cause severe and progressive damage many years after exposure (at least 15 years for cases 3 and 4), especially when the toxic effects were diminishing or stable during earlier years.

An expansion of atrophic lesions over time can occur in diseases unrelated to drugs, such as age related maculopathy and the 'creep' of retinal pigment epithelial (RPE) atrophy[17,18] that occurs months to years after macular photocoagulation. It is possible that in late thioridazine toxicity we are seeing the non-specific expansion of scars, equivalent to the late exposure of areas of subclinical drug induced RPE damage that occurred at the time of original drug usage. Thioridazine probably injures cells over larger areas of RPE than are visible initially by ophthalmoscopy or angiography. These areas of marginal injury may decompensate or degenerate years later when time and age related pathology take their toll. At least one author has asked whether similar arguments may apply to chloroquine retinopathy.[19] In thioridazine cases with relatively mild initial damage (such as cases 2 and 4), the prognosis over the long term is probably fairly good; in patients in whom there is more widespread damage in the early years (such as cases 1, 3, and 7) the prognosis will be much more guarded, since decompensation of the compromised RPE could eventually lead to diffuse atrophy.

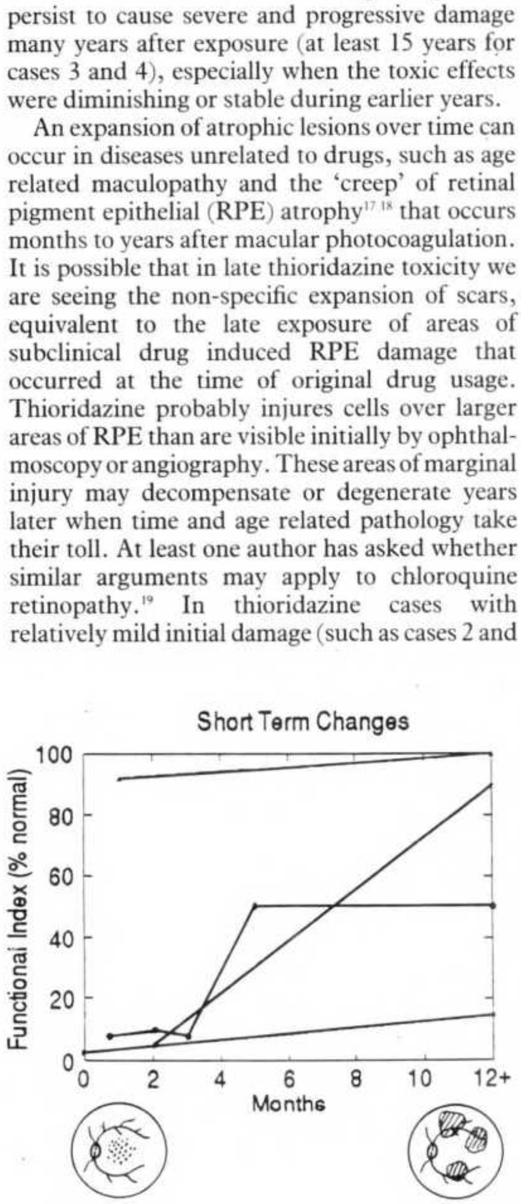


Figure 3 Diagram of functional status (short-term) during the first year after thioridazine exposure for cases 1–4. The 'functional index' represents a composite of available ERG dark adaptation and visual field data normalised between absent (0%) and normal (100%) function. This index is only a schematic device to demonstrate trends of improvement or regression (the actual data for each case are given in Table 1).

Until the late pigmentary and functional changes in thioridazine can be clearly shown to be a result of continued drug action I suggest that thioridazine toxicity *not* be referred to as a progressive chorioretinopathy. That term carries an implication of monotonic functional decline from a primary disease process. There is no question that many cases of thioridazine retinopathy show late deterioration; however, the examples in this paper show that the early fundus changes from granular to nummular retinopathy do not correlate with a 'progression' of visual loss (indeed, vision typically *improves*), and the late atrophic fundus changes are variable in onset and may represent a secondary decompensation. There is unquestionably a risk of late atrophic degeneration, but the cause of this retinopathy is complex, and it may not always progress.

These conclusions have important clinical implications. First, in thioridazine toxicity (and indeed retinal disease in general) pigmentary scarring is not necessarily equivalent to functional damage. Patients with thioridazine toxicity must be followed up with functional tests such as visual field and the ERG, in addition to observation of the fundus, if progression and toxicity is to be assessed accurately. Secondly, the fact that severe late loss of function does occur in occasional individuals indicates that patients with thioridazine toxicity need to be followed up indefinitely to document the stability or progression of disease. Thirdly, the hypothesis that subclinical damage may exist at the time of initial toxic exposure suggests a possible therapeutic strategy. Ischaemic damage to the retina can be minimised by treatment with dextromethorphan,[20] which blocks the secondary death of marginally injured cells by the release of excitatory amino acids. If agents can eventually be found that reduce the amount of secondary RPE decompensation after thioridazine exposure, the long term visual risks would be greatly reduced.

Case 5 reminds us of an additional caveat: functional tests may be influenced by nonorganic factors. Many patients using thioridazine have psychiatric disease, and their subjective

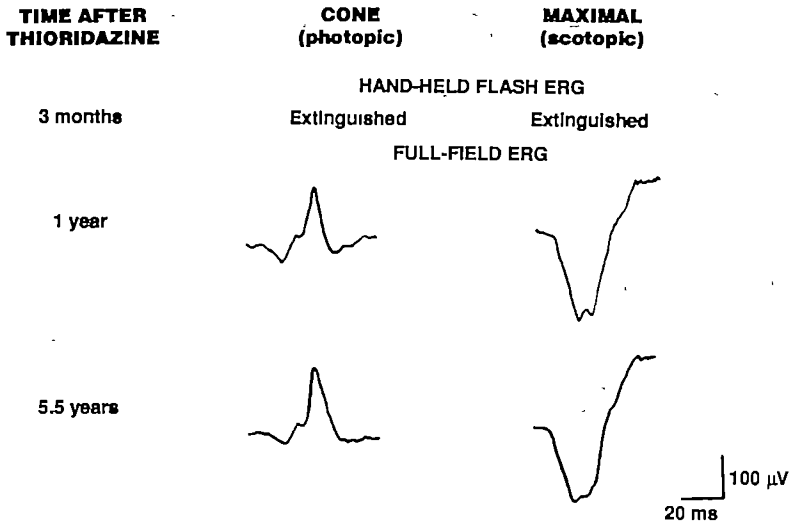


Figure 4 Electroretinograms from case 2, recorded at intervals after stopping thioridazine.

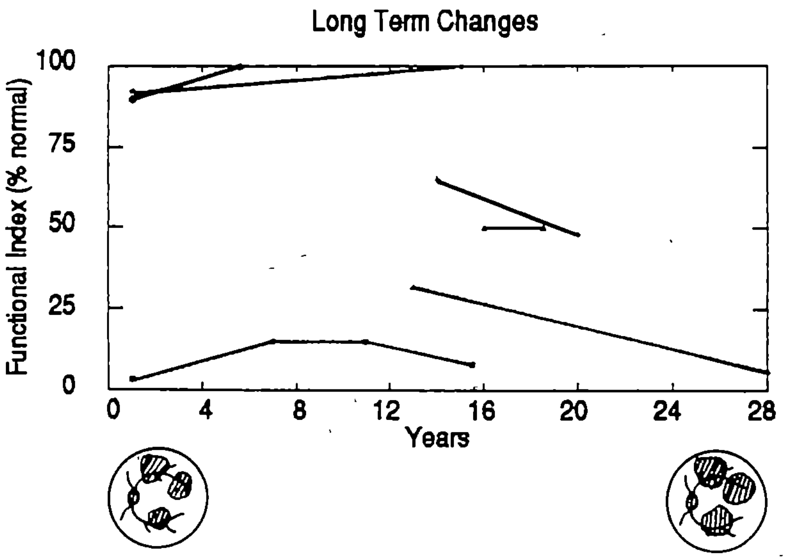


Figure 5 Diagram of functional status (long-term) more than one year after thioridazine exposure for cases 2–7. Functional index is defined as in Fig 3.

responses may vary with mental status and/or secondary gain. If objective measures such as fundus photography and ERG had not been performed repeatedly on case 5, a very convincing story for progressive retinopathy might have been made. Psychophysical tests may be sufficient for routine follow-up when there is no progression of visual symptoms, but it is important to have a baseline of objective data at the time of initial diagnosis to allow for later comparisons that may be needed.

This work was supported in part by NIH-NEI Research Grant EY01678, and an unrestricted grant from Research to Prevent Blindness, Inc.

1 Weekley RD, Potts AM, Reboton J, May RH Pigmentary retinopathy in patients receiving high doses of a new phenothiazine. *Arch Ophthalmol* 1960; 64: 95–106.
2 Zinn K, Marmor MF. Clinical toxicology of the retinal pigment epithelium. In Zinn K, Marmor MF, eds. *The retinal pigment epithelium.* Cambridge: Harvard University Press, 1979: 381–94
3 Davidorf FH. Thioridazine pigmentary retinopathy. *Arch Ophthalmol* 1973; 90: 251–5.
4 Cohen J, Wells J, Borda R Thioridazine (Mellaril) ocular toxicity. *Doc Ophthalmol Proc Ser* 1978; 15: 91–4.
5 Potts AM. Drug-induced macular disease. *Ophthalmology* 1966; 70: 1054–7
6 Kozy D, Doft BH, Lipkowitz J. Nummular thioridazine retinopathy *Retina* 1984; 4: 253–6.
7 Meredith TA, Aaberg TM, Willerson WD. Progressive chorioretinopathy after receiving thioridazine. *Arch Ophthalmol* 1978; 96: 1172–6
8 Ogawa S, Kurumatani N, Schibaike N, Yamazoe S. Progression of retinopathy long after cessation of chloroquine therapy *Lancet* 1979; i. 1408.
9 Schmoger E, Muller W, Haase E. Follow-up in a case of retinopathy more than 10 years after stopping chloroquine therapy *Doc Ophthalmol Proc Ser* 1978; 15: 101–5.
10 Sassani JW, Brucker AJ, Cobbs W, Campbell C Progressive chloroquine retinopathy *Ann Ophthalmol* 1983; 15: 19–22.
11 Ehrenfeld M, Nesher R, Merin S. Delayed-onset chloroquine retinopathy *Br J Ophthalmol* 1986; 70: 281–3.
12 Leinfelder PJ, Burian HM. Mellaril intoxication of retina with full restitution of function. *Invest Ophthalmol Vis Sci* 1964; 3: 466.
13 Connel MM, Poley BJ, McFarlane JR. Chorioretinopathy associated with thioridazine therapy. *Arch Ophthalmol* 1964; 71: 816–21.
14 Potts AM. The concentration of phenothiazines in the eye of experimental animals. *Invest Ophthalmol Vis Sci* 1962; 1: 522–30.
15 Cerletti A, Meier-Ruge W Toxicological studies on phenothiazine induced retinopathy. In: Baker SB de C, Boissier JR, Koll W, eds. *Proceedings of the European Society for Study of Drug Toxicity.* Amsterdam: Excerpta Medica, 1968. 9: 170–88.
16 Fishman G. Thioridazine hydrochloride (Mellaril) toxic pigmentary chorioretinopathy In: Smith JL, ed. *Neuro-ophthalmology update.* New York: Masson, 1982: 109–18.
17 Shah SS, Schachat AP, Murphy RP, Fine SL The evolution of argon laser photocoagulation scars in patients with the ocular histoplasmosis syndrome. *Arch Ophthalmol* 1988; 106: 1533–6
18 Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. *Ophthalmology* 1989; 96: 96–103.
19 Brinkley JR, Dubois EL, Ryan SJ Long-term course of chloroquine retinopathy after cessation of medication. *Am J Ophthalmol* 1979, 88: 1–11.
20 Yoon YH, Marmor MF Dextromethorphan enhances ERG recovery after retinal ischemia *Arch Ophthalmol* 1989; 107: 409–11.

British Journal of Ophthalmology, 1990, 74, 743–747

Diode laser trabeculoplasty (DLT) for primary open-angle glaucoma and ocular hypertension

Dominic McHugh, John Marshall, Timothy J ffytche, Peter AM Hamilton, Anthony Raven

Department of Clinical Ophthalmology, Institute of Ophthalmology, Judd Street, London WC1H 9QS
D McHugh
J Marshall

Department of Ophthalmology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
T J ffytche

Moorfields Eye Hospital, City Road, London EC1 2PD
P A M Hamilton

Scientific Generics, Kings Court, Kirkwood Road, Cambridge CB4 2PF
A Raven

Correspondence to:
J D A McHugh, Department of Clinical Ophthalmology, Institute of Ophthalmology, Judd Street, London WC1H 9QS.

Accepted for publication 6 September 1990

Abstract

A pilot study has been carried out to examine the efficacy of diode laser trabeculoplasty in the treatment of primary open-angle glaucoma and ocular hypertension. The device used was portable and could be attached to a standard slit-lamp microscope. Powers of 0·8–1·2 W were used, with a spot size of 100 μm and a pulse of 0·20 second. Laser trabeculoplasty carried out on 20 eyes for glaucoma resulted in a mean ocular hypotensive effect of 10·2 mmHG at two weeks after treatment and of 9·55 mmHg at 6 months. It is concluded that diode laser trabeculoplasty is an effective mode of treatment for eyes with open-angle glaucoma or with ocular hypertension.

Primary open-angle glaucoma (POAG) is a common, potentially blinding ocular condition. It is characterised by a raised intraocular pressure (IOP), with secondary damage to the optic nerve, and consequent loss of visual field. Treatment is directed towards lowering the IOP, and the first line of treatment consists in topical medication with an ocular hypotensive, for example timolol, often in conjunction with oral therapy such as acetazolamide. However, the response may be insufficient by pharmacological methods alone.

Laser trabeculoplasty (LTP) for the treatment of uncontrolled glaucoma was first described by Wise and Witter in 1979.[1] It has since become an established treatment, with several studies demonstrating its effectiveness.[2,3] It is a technique whereby a number of laser burns are applied to the trabecular meshwork of the angle of the anterior chamber of the eye. LTP is usually performed with an argon laser, which emits blue-green radiation (wavelength 488–514·5 nm), though a similar ocular hypotensive action has been demonstrated with krypton red (647 nm)[4] and neodymium-YAG (1064 nm) laser radiation.[5]

In the present study a portable semiconductor diode laser, emitting at 810 nm, was used to examine the clinical effects of near-infrared irradiation of the trabecular meshwork. The purpose of this study was to evaluate the ocular hypotensive action of diode laser trabeculoplasty (DLT) in the treatment of patients with primary open-angle glaucoma. In this preliminary investigation randomised comparison with argon laser trabeculoplasty was not performed.

Materials and methods

INSTRUMENTATION

A diode laser was used in the study which could be attached to a standard Haag-Streit slit-lamp. The maximum available power of the infrared treatment beam was 1·4 W. The aiming beam was provided by a low-power, red-emitting laser diode. When it was not in use the laser could be stored in a carrying case, which enabled treatments to be carried out at two centres with the same instrument. A more detailed description of the laser is provided elsewhere.[6]

INCLUSION CRITERIA FOR PATIENTS

Patients were recruited to the study from general clinics at Moorfields Eye Hospital and from the Department of Ophthalmology at St Thomas's Hospital. The following inclusion criteria were established for the study:

(*a*) The patient should have primary open-angle glaucoma for which medical therapy had failed to satisfactorily control intraocular pressures. Because the emphasis of the study was directed at the effect on IOP, patients with poorly controlled ocular hypertension but no visual field abnormalities were also admitted to the study. Patients with forms of secondary glaucoma – for example, resulting from uveitis, or aphakia were excluded.

(*b*) The pretreatment IOP should be 22 mmHg or greater.

(*c*) The patient should be able to provide informed consent to participate in the study and be willing and able to attend for follow-up visits.

(*d*) There should be no corneal opacities, such as band keratopathy, that precluded adequate visualisation of the trabecular meshwork.

(*e*) No previous photocoagulation or operative surgery should have been performed on the trabecular meshwork.

PATIENT EVALUATION

Pretreatment evaluation of the patient consisted of:

(*a*) Corrected visual acuity with an illuminated Snellen chart at 6 metres.

(*b*) Biomicroscopic examination of the anterior segment, including: Intraocular pressure measurement with a Goldmann applanation tonometer. All measurements of IOP were performed in the morning. Gonioscopy using a Goldmann 3-mirror contact lens. The width of the anterior chamber angle was estimated on a scale of 0–4 on the Shaffer grading. Funduscopy included an examination of the optic discs, with an estimation of the cup:disc ratio and the degree and extent of pallor. Colour stereo photographs of the optic discs were taken in those eyes without pharmacologically induced miosis.

TREATMENT PROTOCOL

All patients were given a full explanation of the treatment and possible side effects before signing consent forms. Included in the discussion was a statement that some discomfort may be associated with the treatment. Therapy was carried out on a separate day from that of the pretreatment assessment. No adjustment was made to the patient's glaucoma medication prior to laser therapy.

Twenty eyes in 13 patients were treated. Sixteen eyes had chronic open-angle glaucoma, three eyes had ocular hypertension (with raised intraocular pressures but normal visual fields), and one eye had pseudoexfoliation glaucoma. Eight patients were female and five male. Two patients were black, the others were Caucasian. The mean age was 65 (range 57–76).

After instillation of a topical anaesthetic (amethocaine 1%), a Goldmann or Ritch contact lens was applied to the eye in order to allow visualisation of the anterior chamber angle. All treatments were performed throughout the study by one clinician (DM), who had prior experience in the use of lasers for the management of glaucoma. The pattern of treatment consisted in applying approximately 50 burns to 180° of the trabecular meshwork, The laser spot size was 100 μm and the pulse duration was 0·20 second. The target area was the pigmented portion of the trabecular meshwork. The power was adjusted to produce a mild blanching of the trabecular meshwork.

The intraocular pressures were measured two to three hours after therapy. A transient rise in pressure would be treated with a drop of timolol 0·5%. The patients were asked to continue with their current glaucoma medication.

POST-TREATMENT REVIEW

The patients were reviewed at two weeks, six weeks, and 12 weeks after treatment and at two- to three-month intervals thereafter. At each visit the ocular examination included measurement of visual acuity, anterior segment examination, intraocular pressures and funduscopy, including examination of the optic discs.

If a satisfactory ocular hypotensive effect was achieved, with the IOP less than 22 mmHG, a reduction of the patient's ocular medication was considered.

An unsatisfactory response to treatment was considered to be failure of the intraocular pressure to fall to less than 22 mmHg at six weeks after laser therapy. In this case laser trabeculoplasty was repeated to the other 180° of the angle. Continued failure to control the IOP would lead to consideration of operative intervention.

Table 1 Changes in intraocular pressure induced by diode laser trabeculoplasty (DLT)

Mean pretreatment IOP (mmHg)	28·30 (SD=3·63) (n=20)
Mean IOP at 2 weeks following DLT	18·10 (SD=2·53) (n=20)
Mean reduction in IOP at 2 weeks	10·20 (SD=3·25) (p=<0·001)
Mean IOP at 6 weeks following DLT	19·10 (SD=2·88) (n=20)
Mean reduction in IOP at 6 weeks	9·20 (SD=4·48) (p=<0·001)
Mean IOP at 3 months following DLT	19·00 (SD=3·63) (n=20)
Mean reduction in IOP at 3 months	9·30 (SD=4·70) (p=<0·001)
Mean IOP at 6 months following DLT	18·75 (SD=3·11) (n=20)
Mean reduction in IOP at 6 months	9·55 (SD=3·36) (p=<0·001)

Table 2 Mean reduction in IOP following diode laser trabeculoplasty in comparison with treatment with other lasers

Laser treatment	*Reduction in IOP at 2–4 weeks (mmHg)*	*Reduction in IOP at 4–6 weeks (mmHg)*
Diode	10·2 (n=20)	9·20 (n=20)
Argon*	6·9 (n=26)	9·7 (n=34)
Argon†	4·0 (n=61)	5·5 (n=61)
cw.Nd-YAG‡	6·2 (n=33)	6·3 (n=33)

*From Schwartz *et al.*[2]
†From Fink *et al.*[16]
‡From Belgrado *et al.*[5]

Results

USE OF INSTRUMENTS

No problems were encountered with the slit-lamp mountable version of the diode laser in conjunction with a Goldmann 3-mirror or a Ritch lens. Visualisation of the angle of the anterior chamber was not difficult, and the red aiming beam was easily focused on the trabecular meshwork.

LASER BURNS

The tissue reaction that was commonly observed following laser exposure was a blanching of the pigmented portion of the trabecular meshwork. This generally occurred at power settings of between 800 and 1200 mW. In eyes with poor trabecular pigmentation this response was more difficult to identify. Formation of gas bubbles at the site of laser irradiation was not observed.

CLINICAL RESULTS

The mean period of review was eight months (range 6–12 months). Seven patients had bilateral DLT, and six had treatment to one eye only. Sixteen eyes had one treatment with the diode laser, and four eyes had two treatments.

Intraocular pressures. The mean pretreatment intraocular pressure was 28·3 mmHg (range 22–36). The mean IOP two weeks after laser trabeculoplasty was 18·1 mmHg (range 14–22). It was noted that in three of the six patients who had treatment to one eye the intraocular pressure was lower in the untreated eye than before treatment (by 3, 4, and 8 mmHg). In the remaining untreated eyes there was no change in intraocular pressure.

Table 1 shows that the ocular hypotensive effect of laser therapy was maintained in the treatment group over a period of six months following treatment. The paired *t* test, which determines the difference between matched samples, was used to assess changes in IOP from the baseline pretreatment level. The results indicate that therapy was associated with a significant reduction in intraocular pressure, which was maintained over the period of review. Table 2 allows historical comparison with results from previous studies which utilised other laser wavelengths for trabecular irradiation. Fig 1 and 2 illustrate the IOPs before and at (Fig 1) two weeks and (Fig 2) six months following treatment in each of the eyes. Of the five eyes which have been reviewed for longer than six months four have had IOPs of less than 22 mmHg. One

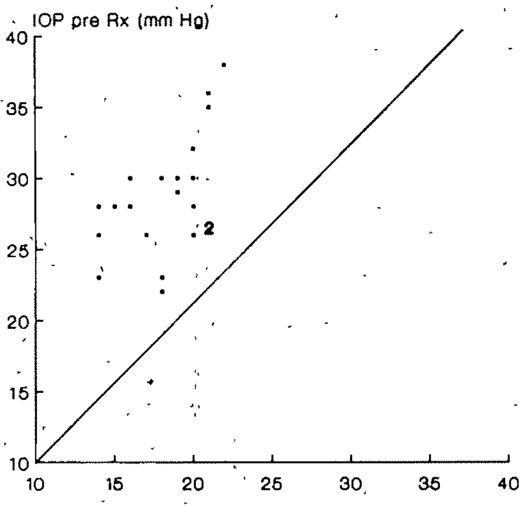


Figure 1 Intraocular pressures before and at two weeks after diode laser trabeculoplasty (20 eyes). Treatment was associated with a reduction in pressure ranging from 4 to 14 mmHg. Rx=treatment.

eye had a measured pressure of 25 mmHg at 10 months and evidence of further loss of visual field. It was therefore decided to perform a trabeculectomy on this patient.

In this small series no particular factors were identified which would tend to reduce the success of treatment. One of the black patients treated had an initial reduction in IOP from 28, 22 mmHg, to 16, 18 mmHg at two weeks. At six weeks and 24 weeks following treatment the pressures had been 20, 18, and 21, 19 mmHg. Any further increase of IOP in the right eye will require a second trabeculoplasty to be carried out.

Two patients had their hypotensive medication adjusted. One patient had returned four weeks after treatment to both eyes. She had suffered a myocardial infarction and her glaucoma medication of acetazolamide 250 mg four times a day, pilocarpine 4% four times a day, and timolol 0·25% twice a day had been stopped. On examination her intraocular pressures were 36 and 38 mmHg. DLT was repeated to each eye and the patient was started on pilocarpine 4% eye drops. Two weeks later her intraocular pressures were 22 mmHg in each eye, and six weeks after therapy they were 21 mmHg bilaterally. The second patient had pretreatment pressures of 28 mmHg bilaterally and was being treated with adrenaline 1% eye drops and timolol 0·5% eye drops twice daily to each eye, in addition to acetazolamide 250 mg four times a day. Three months after treatment his IOPs were 15 and 14 mmHg. The adrenaline drops were stopped and the dose of acetazolamide was reduced to 250 mg twice a day. At five months the pressures were well controlled at 16 mmHg in each eye.

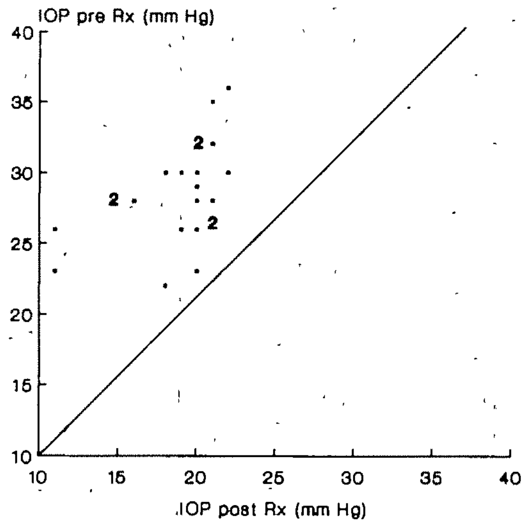


Figure 2 Intraocular pressures before and at six months after diode laser trabeculoplasty (20 eyes). The ocular hypotensive effect of laser treatment appears to have been maintained. Rx=treatment.

Visual acuity. There was no change in visual acuity in any of the patients during the period of review.

Optic discs. During the relatively brief follow-up there was no change in the appearances of the optic discs in the eyes treated.

Complications of therapy. In four of the eyes treated a mild cellular reaction in the anterior chamber was noted two hours after therapy. This was not considered to require anti-inflammatory treatment.

In no eyes was there an acute increase in IOP over pretreatment levels. In six eyes there was a small decrease in IOP. This was attributed to the effect of the contact lens pressing on the eye and resulting in expulsion of aqueous.

Several patients noted a mild 'pricking' sensation during therapy, but no patients complained of excessive discomfort.

Discussion

It is difficult to draw clear-cut conclusions from this study owing to the small size of the treatment group and the limited period of review. Historical comparisons may be made with results from previous studies in order to gain some indications of the efficacy of diode laser trabeculoplasty compared with other forms of laser treatment.

Although LTP is usually performed with an argon laser,[1-3] a similar ocular hypotensive action has been demonstrated with lasers emitting at other wavelengths. Spurney and Lederer[4] reported performing laser trabeculoplasty with a krypton red (647 nm) or krypton yellow laser. A mean reduction in IOP of 9·6 mmHg followed krypton red therapy and 7·0 mmHg after krypton yellow treatment.

A study in which the effects of LTP were compared using a cw neodymium-YAG (1064 nm) laser and an argon blue-green laser showed similar therapeutic effects, though the short pulse duration of the YAG laser (20 ms) rendered the results not strictly comparable.[5]

Table 2 compares the results of the present study with those reported in previous trials at up to two months after treatment. It shows that the early therapeutic effects of LTP are similar and that they do not appear to depend on the wavelength of the laser employed, though there is some indication that diode infrared irradiation tends to effect a greater early reduction in pressure than argon blue laser treatment.

The precise mechanism for the pressure

lowering effect of LTP is unknown. One theory suggests that photocoagulation results in contraction of trabecular fibres, which opens Schlemm's canal by drawing the attached trabecular fibres inward.[7] Another proposes that laser irradiation causes degenerative decay of the trabecular fibres, with a secondary widening of the intertrabecular spaces.[8] Whatever the mechanism of action, it is agreed that the beneficial effect of LTP is to cause a decrease in resistance to aqueous outflow[9] and an improvement in aqueous outflow facility.[2,10] There is also evidence to suggest a more complex biological response to irradiation, with an increase in trabecular cell division, which may also influence the outflow facility.[11]

The observation of a comparable hypotensive effect of diode laser trabeculoplasty with treatment by lasers of other wavelengths implies a similar mode of action. The deeper penetration of infrared into the relatively poorly pigmented trabecular meshwork than with argon blue has been observed in a recent histological study.[12] Possibly this results in a more marked effect on intraocular pressure, either through a greater degree of opening of the trabecular spaces or in promoting more widespread division of those trabecular cells which may play an active role of aqueous outflow.[13] The validity of this speculation awaits the results of further investigations.

The desired visible end point of a trabecular exposure was a mild blanching of the pigmented portion of the trabecular meshwork. This was based on the responses noted during histopathological studies.[12] Gas bubble formation was not a feature of any reaction. This may be related to the characteristics of the tissue response to infrared irradiation, in that the dissipation of energy over a greater path length results in a lower posibility of explosive tissue disruption. Alternatively, it may be due to the powers selected being below the threshold required for formation of gas bubbles.

It is a feature of the treatment protocol of several series that gas bubble formation should be caused as part of the end point.[2,10] The rationale for this has never been satisfactorily explained. Indeed there is some evidence that it has an adverse effect on the eye. It is recognised that LTP is often accompanied by a transient rise in intraocular pressure.[14] This phenomenon may put any eye which is already compromised at risk of further loss of visual field.[15]

The present study with the diode laser found no acute rise in IOP following therapy in any of the eyes treated, even in those eyes with deeply pigmented trabeculae – for example, in black patients. As the desired reaction was to produce a mild blanching of the trabecular meshwork with each burn and bubble formation was not a feature of the exposures, it seems clear that the lesions were only just above threshold in character. There would then be a reduced likelihood of excessive damage to trabecular fibres and of obstruction to aqueous outflow. The mildness of anterior segment inflammation following therapy may also be related to the powers employed in treatment.

Without a detailed knowledge of the mechanisms underlying laser trabeculoplasty it is difficult to optimise the procedure; but clearly the beneficial effects of laser trabeculoplasty do not depend on excessive irradiation of the trabecular meshwork. One study treated patients with argon LTP, with one group being treated with 100 burns at 1 W, and the other group being treated with 65 burns at 850 mW. No significant difference was found in the rate of success for each group.[16] Tissue culture experiments have been performed in which cat trabecular meshwork was irradiated with an argon laser at power settings of 300 mW and at 1000 mW, with no differences being found in the rate of induced cell division between the two groups.[17]

The powers used in the present study were of the order of 1 watt and therefore similar to those used with argon LTP. However, the lower absorption of infrared (810 nm) within melanin compared with that of argon blue-green radiation (488–514·5 nm)[18] implies less energy deposition with diode irradiation at comparable power levels. This should lead to less tissue damage with diode exposures, but clearly a similar clinical response was observed.

It was interesting that in several patients a reduction in pressure was noted in the contralateral, untreated eye. This was described by Fink *et al*,[19] in their series of 34 eyes. They found an average decrease of 4·2 mmHg in the untreated eyes compared with 9·9 mmHg in the treated eyes. This raises the possibility of the influence of neurogenic factors or systemically disseminated chemical mediators.

The limited review period of the present series does not allow any conclusions to be drawn regarding the longer term efficacy of diode laser trabeculoplasty. Previous studies of argon LTP report a maximum pressure lowering effect occurring between two months[20] and 6–9 months after treatment.[16]

Previous studies have demonstrated the clear cut ergonomic advantages of diode lasers over current ion laser systems in relation to their compactness and greater reliability.[6,21] The effectiveness of laser trabeculoplasty (as with other forms of treatment) in slowing the sight threatening consequences of glaucoma has still not been fully established. The present study has, however, shown that infrared diode laser trabeculoplasty is effective in the control of intraocular pressure and that it is a treatment with minimal ocular side effects. It thus represents a sound adjunct to, or replacement of, pharmacological therapy and a means of deferring drainage surgery, with its attendant risk of damage to sight.[22]

We thank Keeler Ltd for providing the diode laser that was used in the study.

J D A McHugh was supported by a grant from the Allerton Vision Research Trust

1 Wise JB, Witter SL. Argon laser therapy for open angle glaucoma: a pilot study. *Arch Ophthalmol* 1979; 97: 319–22.
2 Schwartz AL, Whitten ME, Bleimen B, *et al* Argon laser trabecular surgery in uncontrolled phakic open-angle glaucoma. *Ophthalmology* 1981; 88: 203–12.
3 Pollack IP, Robin AL, Sax H The effect of argon laser trabeculoplasty under medical control of primary open angle glaucoma. *Ophthalmology* 1983; 90: 785–9.
4 Spurny RC, Lederer CM Jr Krypton laser trabeculoplasty: a clinical report. *Arch Ophthalmol* 1984; 102: 1626–8

5 Belgrado G, Brihaye-Van Geertruyden, Herzeel R. Comparison of argon and cw.Nd:YAG laser trabeculoplasty. Clinical results In: Marshall J. ed. *Laser technology in ophthalmology.* Berkeley: Kugler, Ghedini, 1988: 45–8.

6 McHugh JDA, Marshall J, ffytche TJ, Hamilton AM, Raven A, Keeler CR Initial clinical experience using a diode laser in the treatment of retinal vascular disease. *Eye* 1989; **3**: 516–27.

7 Weber PA, Davidorf FH, McDonald C. Scanning electron microscopy of argon laser trabeculoplasty. *Ophthalmic Forum* 1983; **1**: 26–9.

8 Van der Zypen E, Fankhouser F. Ultrastructural changes of the trabecular meshwork of the monkey (*Macaca speciosa*) following irradiation with argon laser light. *Graefes Arch Clin Exp Ophthalmol* 1984; **221**: 249–61.

9 Brubaker RF, Liesegang TJ. Effect of trabecular photocoagulation on the aqueous humor: dynamics of the human eye. *Am J Ophthalmol* 1983; **96**: 139–47.

10 Wilensky JT, Jampol LM. Laser therapy for open-angle glaucoma. *Ophthalmology* 1981; **88**: 213–7.

11 Bylsma SS, Samples JR, Acott TS, Van Budkirk EM. Repopulation of the trabecular meshwork after argon laser trabeculoplasty. *Invest Ophthalmol Vis Sci* 1988; **29** (suppl): 129.

12 McHugh JDA, Marshall J, ffytche TJ, Hamilton AM, Raven A. Diode laser trabeculoplasty (DLT) for chronic simple glaucoma. *Invest Ophthalmol Vis Sci* 1990; **31** (suppl): 340

13 Bylsma SS, Samples JR, Acott TS, Van Buskirk EM. Trabecular cell division following argon laser trabeculoplasty. *Arch Ophthalmol* 1988; **106**: 544–7.

14 Weinreb RN, Ruderman J, Juster R, Sweig K. Immediate intraocular pressure response to argon laser trabeculoplasty. *Am J Ophthalmol* 1983; **95**: 279–86

15 Levene R. Major early complications of argon laser trabeculoplasty *Ophthalmic Surg* 1983; **14**: 947–53

16 Fink AI, Jordan AJ, Lao PN, Fong DA Therapeutic limitations of argon laser trabeculoplasty. *Br J Ophthalmol* 1988; **72**: 263–9.

17 Bylsma SS, Pirouzkar B, Acott TS, Van Buskirk EM, Samples JR. In-vivo cell division after argon laser trabeculoplasty. *Invest Ophthalmol Vis Sci* 1989; **30** (suppl) 280

18 Gabel VP, Birngruber R, Hillenkamp F Individuelle Unterscheide der Lichtabsorption am Augenhintergrund in sichtbaren und infraroten Spectralbereich *Ber Dtsch Ophthalmol Ges* 1977; **47**: 418–21

19 Fink AI, Jordan AJ, Bunke A, Fong DA. Argon laser trabeculoplasty as an alternative to carbonic anhydrase therapy. *Trans Ophthalmol Soc UK* 1982; **102**· 125–8

20 Schwartz AL, Love DC, Schwartz MA. Long-term follow-up of argon laser trabeculoplasty for uncontrolled open-angle glaucoma *Arch Ophthalmol* 1985; **103**: 1482–4.

21 McHugh JDA, Marshall J, Capon M, *et al.* Transpupillary photocoagulation in the eyes of rabbit and human using a diode laser *Lasers Light Ophthalmol* 1988; **2**: 125–43.

22 Watson PG, Grierson I. The place of trabeculectomy in the treatment of glaucoma. *Ophthalmology* 1981; **88**: 175–96

British Journal of Ophthalmology, 1990, **74**, 748–749

CASE REPORTS

Atraumatic iris cilia

G I S Mackintosh, M C Grayson

Department of Ophthalmology, Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA
G I S Mackintosh

Victoria Hospital, Kirkaldy, Fife KY2 5AH
M C Grayson

Correspondence to:
Mr G Mackintosh.

Accepted for publication
14 June 1990

*I thank Dr D Charteris and Professor W R Lee, of the Tennent Institute of Ophthalmology, Western Infirmary, Glasgow.

Abstract

We report two cases of ectopic cilia originating from the iris without any convincing history of injury to the eye. One required surgical removal to prevent further endothelial and lens damage developing over a five-year observation period.

Eyelashes implanted into the iris following an injury have been reported on a number of occasions.[1] The ballistics are difficult to envisage, but the projectile may remove several lashes from the lid margin together with a small piece of skin and transport this to the iris, into which it becomes implanted. The projectile is subsequently withdrawn or falls out, leaving the lashes behind, and the corneoscleral wound may be quite small. The mechanism is well documented.[1]

This, however, may not be the only means by which lashes can be found emerging from the iris into the anterior chamber and we report two cases suggesting a different origin.

Case reports

CASE 1

On 2 March 1981 a 16-year-old female was referred by her optician with a history of mild intermittent pain in her left eye over the preceding months. She was found to have three lashes that appeared to arise from the root of the iris anteriorly and one that emerged through the pupil (Fig 1). Gonioscopy did not reveal any angle recession and did not clarify the site of origin of the lashes. Slit-lamp examination of the superior limbus and sclera did not show any evidence of old corneoscleral scarring (Fig 2).

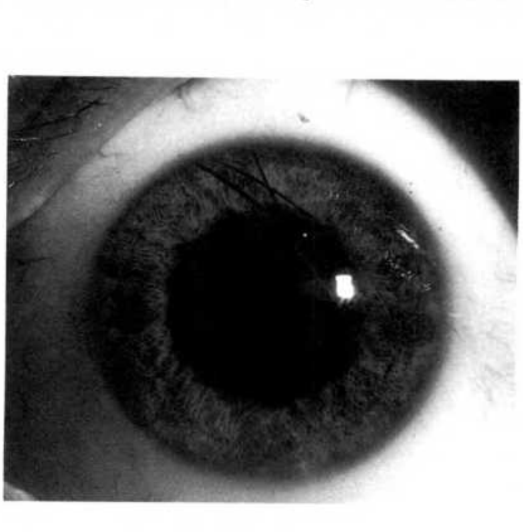


Figure 1 Case 1. Left eye 2 March 1981. The lash emerging through the pupil is not visible.

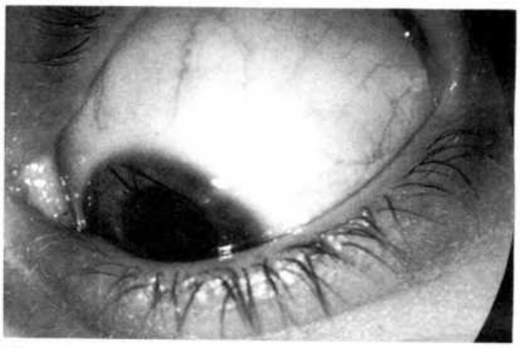


Figure 2 Case 1. Left eye 2 March 1981 showing superior limbus and sclera with no evidence of scarring.

On initial examination the visual acuity was 6/6 unaided right and 6/18 unaided left (6/12 with pinhole). The eye was quiet and required no treatment at that time. At 6 months and one year later no significant change was noted.

She returned four years later on 15 December 1986 because of irritation in the eye, and on this occasion she was found to have developed an early anterior capsular lens opacity plus a central posterior corneal opacity where the internal lashes had rubbed the corneal endothelium (Fig 3). Her visual acuity was 6/5 right and 6/36 left (6/9 corrected).

On 12 February 1987 a sector iridectomy was performed, the lashes were removed, and to date there has been no recurrence nor further problems with the eye.

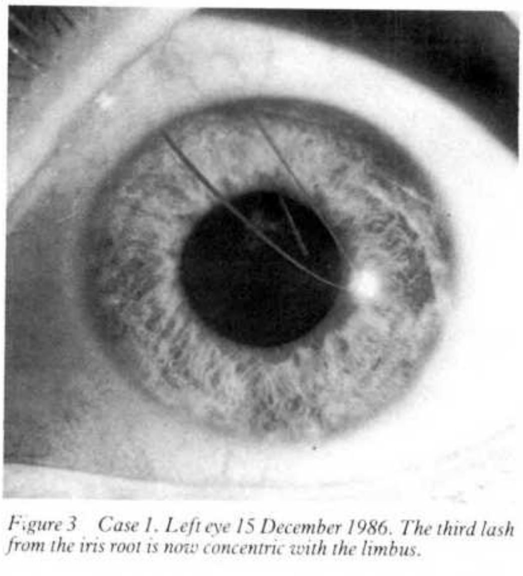


Figure 3 Case 1. Left eye 15 December 1986. The third lash from the iris root is now concentric with the limbus.

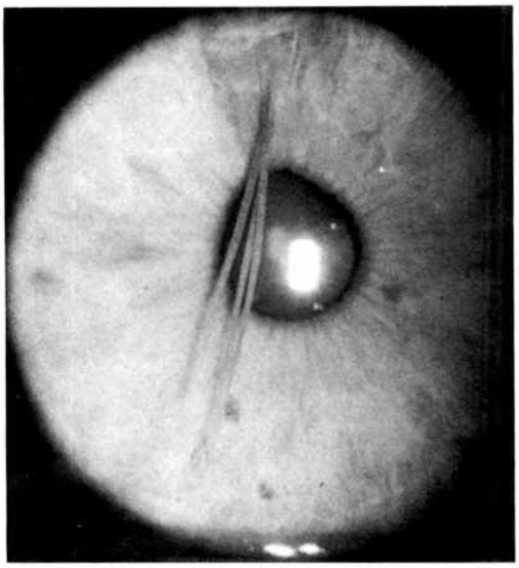


Figure 4 Case 2. Left eye, 21 March 1985.

A histology study* failed to reveal the lash follicles or the origin of the lashes, which may therefore have been more posterior, perhaps from the ciliary body. The cilia became dislodged from the iris tissue during processing and appeared to have a normal lash-like structure, but no follicles were seen on serial section. There was no evidence of teratoma or foreign body granuloma.

CASE 2

On 21 March 1985 a 30-year-old man presented to the ophthalmic casualty department with a small corneal abrasion resulting from a blow to the eye with a piece of wood several hours earlier. On slit-lamp examination it was found that he had three cilia protruding from the iris at the 12 o'clock position (Fig 4). These were not touching the corneal endothelium, and he had no history of pain or irritation in the eye. His acuity was 6/6 right and left unaided.

The patient was examined by GISM and two consultant ophthalmologists, who found no evidence of corneoscleral scarring to indicate a previous perforating injury to account for the lashes. The patient recalled being scratched in the eye 12 years previously by a piece of wire, but the severity of this injury and the lack of evidence of trauma on slit-lamp examination make it difficult to account for the cilia as a result of this accident. The patient was asked to attend for review but was lost to follow-up, and presumably the cilia have not been causing him any discomfort or visual problems.

Discussion

The origin of the ectopic cilia in these two cases is a mystery. The pathology in case 1 confirmed them to be like ordinary lashes but did not explain their derivation. In this case the lashes either moved or grew in the anterior chamber. We did not measure their length, but they appeared to be both longer and in new positions, causing damage to lens and endothelium and necessitating their removal.

It is difficult to exclude long forgotten childhood accidents, and lashes have been discovered implanted in the iris years after the original injury.[1-3] But the absence of any history of previous trauma in case 1 and the history of only mild trauma in case 2 plus the lack of corneoscleral scarring on slit-lamp examination makes it difficult to believe that the lashes were implanted as a result of an accident. This is in accord with the personal experience of one of us (GISM), who has observed an eye injury resulting in lashes implanted into the iris. In this case (unpublished) the lashes were removed from the lid margin by the recoil of a piece of wire and implanted into the iris through a corneosclaral laceration several millimetres long. The wound required suturing and the injury resulted in a severe and chronic inflammatory reaction despite removal of the lashes.

How then can an ectodermal structure develop from mesoderm and neuroderm? Hair has been described both in dermoids and teratomata.[4-6] Epibulbar dermoids have been described containing hair, which in one case grew through the conjunctiva.[7] Dermoids have also been described invading the iris,[7] and these cilia can grow at puberty.

Possibly the ectopic cilia in the two cases described were part of a dermoid cyst or teratoma, and some of the previously described cases of lashes in the anterior chamber with no good evidence of trauma may also fall into this category. The specimen of iris for histology in case 1 showed only normal iris tissue, but this may have been because the lashes arose from a dermoid or teratoma situated more posteriorly in the ciliary body or sclera, and this was not excised.

These cases question the assumption that all intraocular cilia must have been derived from trauma.

1 Duke-Elder S. *Textbook of ophthalmology*. London: Kimpton, 1972; **14** (1); 553–9.

2 Joseph AL. Cilia in the anterior chamber: report of a case. *Ear Nose Throat J* 1967; **46**: 188–9.

3 Hughes RA. A cilium thru the iris without symptoms. *Am J Ophthalmol* 1924; 7: 702.

4 Greer CH. *Ocular pathology*. 3rd ed. London: Blackwell, 1979: 223.

5 Spencer WH. *Ophthalmic pathology: an atlas and textbook*. Philadelphia: Sanders, 1986; **3**: 2489–93.

6 Yanoff M, Fine B. *Ocular pathology: a text and atlas*. Hagerstown: Harper and Row, 1975: 516–26.

7 Duke-Elder S. *Textbook of ophthalmology*. London: Kimpton, 1964; **3** (2): 820–3.

British Journal of Ophthalmology, 1990, **74**, 750

Infectious mononucleosis presenting as bilateral acute dacryocystitis

P L Atkinson, A M Ansons, A Patterson

Royal Liverpool Children's Hospital, Alder Hey, Eaton Road, Liverpool L12 2AP
P L Atkinson
A M Ansons
A Patterson

Correspondence to:
Mr P L Atkinson, St Paul's Eye Hospital, Old Hall Street, Liverpool L3 9PF.

Accepted for publication
26 April 1990

Abstract

A case of infectious mononucleosis presenting as bilateral acute dacryocystitis in a 7-year-old girl is reported. Acute dacryocystitis is uncommon in this age group, and an underlying systemic illness should be suspected particularly when it is bilateral.

We report a case of infectious mononucleosis in a child presenting as bilateral acute dacryocystitis.

Case report

A previously well 7-year-old girl presented with one week's history of malaise, sore throat, and watering eyes. Four days before presentation the eyelids on the left had become swollen, and the eye become red with a purulent discharge. The right eyelids had swollen to a lesser extent. There was no previous history of eye problems; in particular no previous epiphora.

Examination showed bilateral periorbital oedema with bilateral conjunctival injection. Both lacrimal sacs were tender and swollen, more markedly on the left (Figure 1). There was a purulent discharge from the left eye. On applying gentle pressure, mucopurulent material was expressed from the right lacrimal sac.

The patient was pale and lethargic, with a mild pyrexia (37·5°C). Bilateral preauricular and cervical lymphadenopathy and splenomegaly were present. The pharynx was mildly inflamed, with no membrane. The full blood count showed a lymphocytosis (53%) and atypical mononuclear cells. The Paul-Bunnell test was positive. *Streptococcus pneumoniae* was grown from the conjunctival discharge.

Empirical treatment with intravenous ampicillin and flucloxacillin was started when the patient presented, and continued for seven days. The dacryocystitis resolved by the fourth day. The epiphora of both eyes had abated and she felt generally well at discharge on the seventh day.

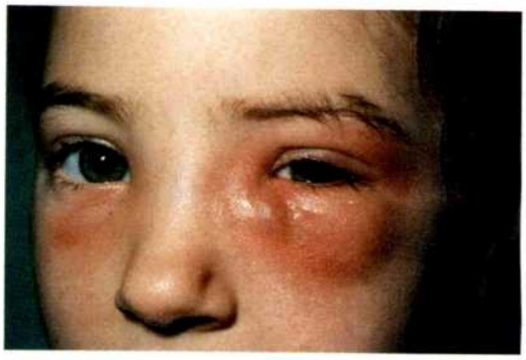


Figure 1 Bilateral dacryocystitis in a girl with infectious mononucleosis.

Discussion

Infectious mononucleosis can present with ocular involvement, most commonly periorbital oedema, lacrimation, and conjunctivitis.[1-3] Unilateral acute dacryocystitis is rare.[4,5] Infectious mononucleosis presenting as bilateral acute dacryocystitis has not been previously reported.

Acute dacryocystitis is usually seen in adults and infants with pre-existing nasolacrimal duct obstruction and is uncommon in previously asymptomatic children. In infectious mononucleosis the generalised lymphoid hyperplasia, particularly in the nasopharynx, may result in nasolacrimal duct obstruction, with lacrimation. The stagnant secretions in the nasolacrimal sac then become secondarily infected.

Infectious mononucleosis should be considered in previously asymptomatic children and young adults presenting with acute dacryocystitis. In such patients the dacryocystitis can be expected to resolve without permanent nasolacrimal duct obstruction.

1 Sumaya CV, Neerhout RC. Sinusitis and periorbital infections complicating infectious mononucleosis. *Am J Dis Child* 1976; **130**: 777.
2 Kouba K, Hlavata E, Karel I. Phlegmonous dacryocystitis and paresis of the soft palate as a rare complication of infectious mononucleosis. *Cesk Oftalmol* 1970; **26**: 181–3.
3 Bessiere E, Agenos B, LeRebeller. Reaction of lacrimal pericystitis during the course of infectious mononucleosis. *J Med Bordeaux* 1962; **139**: 73–5.
4 Tanner OR. Ocular manifestations of infectious mononucleosis. *Arch Ophthalmol* 1954; **51**: 229–41.
5 Stevens JE, Bayrd ED, Heck FJ. Infectious mononucleosis. *Am J Med* 1951; **11**: 202–8.

British Journal of Ophthalmology, 1990, **74**, 751–752

Infestation of extraocular muscle by *Cysticercus cellulosae*

David A DiLoreto, Ross A Kennedy, Janet M Neigel, Jack Rootman

Abstract

Reports of orbital cysticercosis are uncommon despite the high incidence of brain and ocular involvement. Infestation of extraocular muscle is exceedingly rare. Two cases of cysticercosis of the extraocular muscles are reported here. Surgical removal of the encysted parasites successfully resolved the infestation in both cases.

While intraocular infections by *Cysticercus cellulosae* are often found as part of a generalised systemic infestation, ocular adnexal involvement is rare. We report two cases of cysticercosis of an extraocular muscle. The presenting features mimicked subacute orbital myositis in one patient and an orbital tumour in the second.

Case reports

CASE 1

A 35-year-old Cambodian woman was referred to the Orbital Clinic at the University of British Columbia with complaints of right orbital pain and swelling associated with diplopia in lateral gaze. Treatment with topical and systemic antibiotics was ineffective, and the pain had progressed. The visual acuity on both sides was 6/6. There was 4 mm of right proptosis. The right eye movements were limited in abduction and adduction by severe pain. The conjunctiva over the right lateral rectus muscle was injected with inferolateral chemosis. Anterior segment and ocular fundus examination gave normal results. A general physical examination and complete blood count showed normal results, and there was no eosinophilia. B-scan ultrasonogaphy demonstrated a mass within the lateral rectus muscle. Orbital computed tomography revealed a retrobulbar mass with a central lucency involving the right lateral rectus muscle (Fig 1). The differential diagnosis included orbital abscess and tumour. A transconjunctival orbital biopsy was performed laterally. A firm fibrotic mass within an enlarged muscle belly was encountered and removed. Histopathological examination showed a cystic structure lined by a thick fibrous wall containing the parasite *Cysticercus cellulosae* (Fig 2).

Department of Ophthalmology, University of British Columbia, Vancouver, BC, Canada
D A DiLoreto
R A Kennedy
J M Neigel
J Rootman

Correspondence to:
David DiLoreto, MD,
LSU Eye Center,
2020 Gravier Street,
Suite B, New Orleans,
Louisiana 70112 2234, USA.

Accepted for publication
4 December 1989

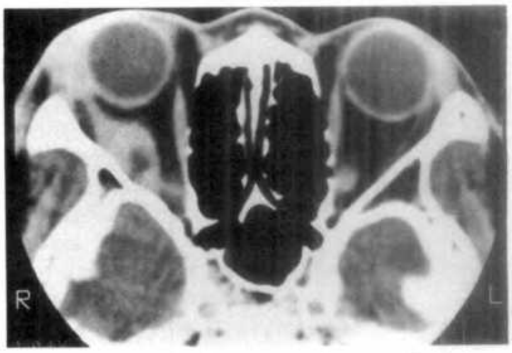


Figure 1: Computed axial tomogram of case one. Orbital mass contiguous with right lateral rectus muscle. Note central lucency.

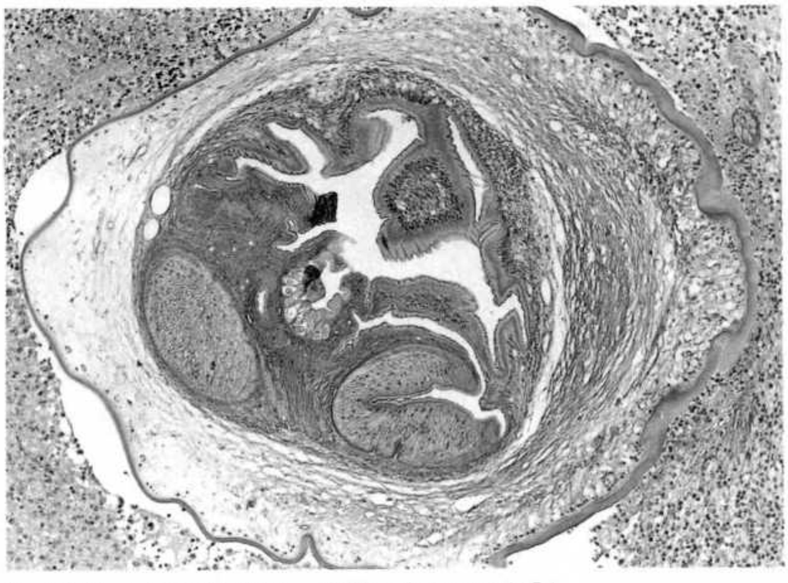


Figure 2: Note scolex with suckers and folding of tegmentum (×7.)

CASE 2

A 7-year-old girl of East Indian origin was seen with complaints of a painless, progressively enlarging epibulbar mass (Fig 3). She had lived in North America her entire life except for a vacation in India one year prior to presentation. Her past medical history was unremarkable, and her visual acuity was 6/6 in both eyes. A 1 cm soft solid mass was present subconjunctively over the left medical rectus muscle. The left globe was displaced laterally without proptosis. Examination of the anterior segment and ocular fundus gave normal results, as did a general

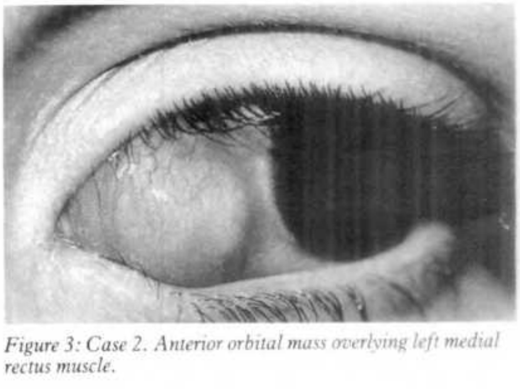


Figure 3: Case 2. Anterior orbital mass overlying left medial rectus muscle.

physical examination. A complete blood count was normal, with no eosinophilia. A CT scan of the orbits showed an enhancing mass of the left medial orbit involving the medial rectus muscle. Because of the possibility of an orbital tumour a transconjunctival exisional biopsy was performed. Histopathological studies of the excised mass revealed a cyst containing a cysticercus surrounded by granulation tissue.

Discussion

Cysticercus cellulosae is the larval form of the pork tapeworm, *Taenia solium*. Man is the only known final host for *T solium*. The organism can remain in the host's intestinal tract causing little or no disturbance. Human cysticercosis is acquired by ingestation of tapeworm eggs shed in faeces. The eggs mature and the larvae penetrate the intestinal muscoa to enter the portal circulation, where they are carried to other organs.[1]

The commonest pattern of systemic involvement is seen in neurocysticercosis and appears as a space occupying intracranial lesion. Treatment is with praziquantel[2] and surgical excision of cysts unresponsive to medical therapy or for relief of intracranial hypertension.[3]

The larval forms may enter the eye through the choroidal circulation and migrate in the subretinal space or enter the vitreous.[4] Death of the larvae within ocular tissues can stimulate severe inflammatory reaction. Such infestations are an important cause of blindness in the endemic areas of South-east Asia, Central America, and Africa. Medical therapy has not proved successful, and treatment is surgical excision.[4-6]

Ocular adnexal infestation in cysticercosis is unusual. Six cases of eyelid involvement have been reported.[7-11] Sen[10] studied four additional cases with orbital involvement. Case reports of infestation of extraocular muscle are exceptional.[12,13] The classical description of orbital cysticercosis is that of an anterior orbital mass with a severe inflammatory reaction.[14] The patients may experience considerable pain accompanied by oedema, chemosis, ptosis, optic neuritis, and restriction of extraocular movements.

Our two cases demonstrate that a variety of clinical features may be seen. The first patient presented with signs of orbital myositis with moderate proptosis due to the posterior location of the cyst. Our second patient lacked inflammatory features and presented with a painless anterior orbital mass.

The diagnosis of cysticercosis can be presumptively established by the presence of small calcific densities on roentgenogram of the skull or extremities. Other tests such as electroencephalography, CT scan, or arteriography may confirm space occupying intraparenchymal brain lesions. Eosinophilia may be present in disseminated disease. Serological testing is often inconclusive, more than 50% of patients with neurocysticercosis having no quantifiable antibody response.[15] Spinal fluid analysis with radioimmunoassay may reveal detectable titres. The diagnosis of non-calcified orbital cysticercosis may be elusive until the cyst is surgically excised. Removal typically results in complete resolution of symptoms, as was the case for both our patients.

Magnetic resonance imaging of neurocysticercosis is well documented.[16] In a recent case of orbital cysticercosis it produced images of cysts in extraocular muscle and outlined a scolex within a cyst.[17] Although additional confirmation is necessary, MR imaging may be the best method of assessing patients with presumed orbital cysticercosis.

1 Dalton HP, Nottebart HC. *Interpretive medical microbiology*. New York: Churchill Livingstone, 1986: 291.

2 Moodley M, Moosa A. Treatment of neurocysticercosis: is praziquantel the new hope? *Lancet* 1989; **i**: 262–3.

3 Robles C, Sedano AM, Vargas-Tentori N, Galdino-Virgen S. Long-term results of praziquantel therapy in neurocysticercosis. *J Neurosurg* 1987; **66**: 359–63.

4 Maschot WA. Intraocular cysticercosis. *Arch Ophthalmol* 1968; **80**: 772–4.

5 Messner KH, Kammerer WS. Intraocular cysticercosis. *Arch Ophthalmol* 1979; **97**: 1103–5.

6 Kestilyn P, Taelman H. Effect of praziquantel on intraocular cysticercosis: a case report. *Br J Ophthalmol* 1985; **69**: 788–90.

7 Jampol LM, Caldwell JBH, Albert DM. *Cysticercus cellulosae* in the eyelid. *Arch Ophthalmol* 1973; **89**: 319–20.

8 Malik SRK, Gupta AK, Choundry S. Ocular cysticercosis. *Am J Ophthalmol* 1968; **66**: 1168–71.

9 Perry HD, Font RL. Cysticercosis of the eyelid. *Arch Ophthalmol* 1978; **96**: 1255–7.

10 Sen DK. *Cysticercus cellulosae* in the eyelid, orbit and lacrimal gland. *Acta Ophthalmol (Kbh)* 1980; **58**: 144–7.

11 Sing G, Kaur J. Cysticercosis of the eyelid. *Ann Ophthalmol* 1982; **14**: 947–50.

12 Brooks AM, Essex WB, West RH. Cysticercosis of superior oblique muscle. *Aust J Ophthalmol* 1983; **11**: 119–22.

13 Rao VA, Kawatra VK, Ratnakar C. Unusual cause of acquired inflammatory Brown's syndrome. *Can J Ophthalmol* 1987; **22**: 320–2.

14 Duke-Elder S. *System of ophthalmology* London: Kimpton 1974; **13**: (2): 929–30.

15 Flisser A, Woodhouse E, Larralde C. Human cysticercosis: antigens, antibodies and non-responders. *Clin Exp Immunol* 1980; **39**: 27–37.

16 Suss RA, Maravilla KR, Thompson J. MR imaging of intracranial cysticercosis: comparison with CT and anatomopathologic features. *AJNR* 1986; **7**: 235–42.

17 Cheung YY, Steinbaum S, Yuh WT, Chiu L. MR findings in extracranial cysticercosis. *J Comput Tomogr* 1987; **11**: 179–81.

VOLUME 41 · AUTHOR INDEX

Abe, S: *see* Shiono, T, etc, 317
Abraham, F A: *see* Cahane, M, etc, 382
Abramson, D H, Servodidio, C A, McCormick, B, Fass, D, Zang, E: Changes in height of choroidal melanomas after plaque therapy, 359
Acheson, R W: *see* Fox, P D, etc, 417
Akingbehin T: *see* Sunder Raj, P, etc, 731
Akyoi, N, Deger, O, Edip Keha, E, Kilic, S: Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract, 661
Al Faran, M F: Visual outcome and complications after cataract extraction in Saudi Arabia, 141
Alghassany, A: *see* Reacher, M H, etc, 109
Al-Haddab, S, Hidayat, A, Tabbara, K F: Ciliary body melanoma with optic nerve invasion, 123
Alhalel, A: *see* Hirsh, A, etc, 638
Al-Kassimi, H: *see* Tabbara, K F, etc, 249
Allan D: *see* Refaat, R F, etc, 254
——: *see* Teoh, Su Lin, etc, 215
Allen, L: *see* Collin, J R O, etc, 542
Amaya, L G, Speedwell, L, Taylor, D: Contact lenses for infant aphakia, 150
Amoni, S S: *see* Babalola, O E, etc, 89
Annesley, W H Jr: *see* Maguire, J I, etc, 556
Ansons, A M: *see* Atkinson, P L, etc, 750
Antle, C M, Damji, K F, White, V A, Rootman, J: Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis, 502
Arden, G B: *see* Falcão-Reis, F, etc, 712
Armitage, W J, Moss, S J, Easty, D L, Bradley, B A: Supply of corneal tissue in the United Kingdom, 685
Arnold, P E: *see* Ingram, R M, etc, 158
Arntz, H R: *see* Wiek, J, etc, 665
Asbell, P A: *see* Weissman, S S, etc, 409
Ashkenazi, I, Cahane, M, Rosen, N (*Correspondence*): A patient's ingenuity in the management of lagophthalmos, 254
——: *see* Cahane, M, etc, 447
Askin, G: *see* West, J, etc, 243
Atkinson, P L, Ansons, A M, Patterson A: Infectious mononucleosis presenting as bilateral acute dacryocystitis, 750
Aurell, E, Norrsell, K: A longitudinal study of children with a family history of strabismus: factors determining the incidence of strabismus, 589
Avni, I: *see* Cahane, M, etc, 447
——: *see* Hirsh, A, etc, 638

Baarsma, G S: *see* de Vries, J, etc, 344
Babalola, O E, Amoni S S, Samila, E, Thaker, U, Darougar, S: An outbreak of acute haemorrhagic conjunctivitis in Kaduna, Nigeria, 89
Backon, J, Matamoros, N, Ramirez, M, Sanchez, R M, Ferrer, J, Brown, A, Ticho, U: A functional vagotomy induced by unilateral forced right nostril breathing decreases intraocular pressure in open and closed angle glaucoma, 607
Baker, A S: *see* Hamady, R, etc, 26
Baldomero, R W: *see* Leff, S R, etc, 498
Baranyovits, P: Stabilisation of refraction following extracapsular cataract extraction, 486
Barker, C, Leitch, J, Brenwald, N P, Farrington M: Mixed haematogenous endophthalmitis caused by *Candida albicans* and CDC fermentative corynebacterium group A-4, 247
Barondes, M, Pauleikhoff, D, Chisholm, I C, Minassian, D, Bird A C: Bilaterality of drusen, 180
Basu, P K: *see* Finkelstein, I, etc, 280
Beare J D L: Eye injuries from assault with chemicals, 514
Behrens-Baumann, W, Klinge, B, Ruchel, R: Topical fluconazole for experimental Candida keratitis in rabbits, 40
Bek, T (*Correspondence*): Diabetes and retinal function, 704
——, Lund-Andersen, H: Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy, 388
Bell, J A (*Correspondence*): Corneal amyloidosis, 320
BenEzra, D, Maftzir, G, de Courten C, Timonen, P: Ocular penetration of cyclosporin A. III. The human eye, 350
Benson, M T, Nelson, M E: Cyclocryotherapy: a review of cases over a 10-year period, 103
——, Rennie, I, Talbot J: External ocular pigmentation secondary to perforating eye injury, 251
van den Berg, W, Verbraaek F D, Bos, P J M: Homocystinuria presenting as central retinal artery occlusion and longstanding thromboembolic disease, 696
Berghout, A: *see* Mourits, M Ph, etc, 481
Berquet, S: *see* Grochowicki, M, etc, 358
Biedner, B Z: *see* David, R, etc, 272
Bigonesse, P: *see* Jotterand, V, etc, 568
Billingham, B: *see* Ingram, R M, etc, 82
Billington, B M: *see* Rose, G E, etc, 160
Bird, A C: *see* Barondes, M, etc, 180
Blackmore, H: *see* Vogel, R, etc, 3
Blake, K D: *see* Russell-Eggitt, I M, etc, 421
Blumenthal, M: *see* Cahane, M, etc, 447
Boen-Tan, T N: *see* de Vries, J, etc, 344
Boisjoly, H M: *see* Jotterand, V, etc, 568
Bos, P J M: *see* van den Berg W, etc, 696
Bosanquet, R C: *see* McKenna, P, etc, 629
Boulton, M: *see* Singh, A, etc, 328
Bradley, B A: *see* Armitage, W J, etc, 685
Brandt, F, Zhou, H M, Shi, Z R, Rai, N, Thuladar, L, Pradhan, H: Histopathological findings in the iris of dapsone treated leprosy patients, 14
Brener, H: *see* Hirsh, A, etc, 638
Brenwald, N P: *see* Barker, C, etc, 247
Briscoe, D: *see* David, R, etc, 272
Brodie, S E, Friedman, A H: Retinal dysfunction as an initial ophthalmic sign in AIDS, 49
Bron, A J: *see* Shun-Shin, G A, etc, 267
——: *see* Smith, G T H, etc, 564
——: *see* Sparrow, J M, etc, 654
Brooks, A M V, Harper, C A, Gillies, W E (*Correspondence*): Malignant glaucoma after laser iridotomy, 576
Brooks, D E: *see* Schulzer, M, etc, 196
Brown, A: *see* Backon, J, etc, 607
Brown, G C: *see* Maguire, J I, etc, 556
Brown, N P: *see* Shun-Shin, G A, etc, 267
Brunner-Ferber, F L: *see* Pfeiffer, N, etc, 405
Buceti, R: *see* Falcão-Reis, F, etc, 712
Buitenhuis, H J: *see* de Vries, J, etc, 344
Bulpitt, C J: *see* Vogel, R, etc, 3
Burchfield, J C: *see* Zalta, A H, etc, 289
Burde, R M: *see* Kellen, R I, etc, 509
Burge, S M: *see* Frith, P, etc, 163
Burke, J P: *see* Leitch, R J, etc, 278
——: *see* West, J, etc, 511

Cahane, M, Ashkenazi, I, Avni, I, Blumenthal, M (*Correspondence*): Total hyphaema following streptokinase administration eight days after cataract extraction, 447
——, Treister, G, Abraham, F A, Melamed, S: Glaucoma in siblings with Morquio syndrome, 382
——: *see* Ashkenazi, I, etc, 254
Canagaratnam, R: *see* Reacher, M H, etc, 109
Carlson, S: *see* Raitta, C, etc, 363
Carmichael, T R, Gelfand, Y, Welsh, N H: Topical steroids in the treatment of central and paracentral corneal ulcers, 528
Carney, L G: *see* Fink, B A, etc, 168
Carter, C J: *see* Schulzer, M, etc, 196
Cartwright, J P: *see* Jenkins, T C A, etc, 681
Castronuovo, S: *see* Collin, J R O, etc, 542
Cennamo, G, Iaccarino, G, de Crecchio, G, Liguori, G: Choroidal osteoma (osseous choristoma): an atypical case, 700
Char, D H, Kroll, S, Stone, R D, Harrie, R, Kerman, B: Ultrasonographic measurement of uveal melanoma thickness: interobserver variability, 183
Charles, S J, Gray, J J: Ocular herpes simplex virus infections: reduced sensitivity to acyclovir in primary disease, 286
Charteris, D G: Progression of an iris melanoma over 41 years, 566
——, Lee, W R: Multifocal posterior uveitis: clinical and pathological findings, 688
Chignell, A H: Pneumoretinopexy: a personal view, 117
——: *see* Rose, G E, etc, 160
Chisholm, I C: *see* Barondes, M, etc, 180
Chowdhury, C R, Wood, C M, Samuel, P R, Richardson, J: Frontal bone epidermoid – a rare cause of proptosis, 445
Christensen, R E: *see* Panek, W C, etc, 223
Clarke, M: *see* West, J, etc, 243
Clarke, M P, Pearson J C G, Vernon, S A, Matthews, J C: Influence of pupil size on measurements made with the Lens Opacity Meter 701, 526
de Clercq, E: *see* Menage, M J, etc, 532
Climenhaga, H: *see* Pe'er, J, etc, 624
Cohen, S M: *see* Lieb, W E, etc, 305
Collin, J R O, Allen, L, Castronuovo, S: Congenital eyelid retraction, 542
Collin, R: *see* Rose, G E, etc, 545
Cook, C D, Hainsworth, M: Tuberculosis of the conjunctiva occurring in association with a neighbouring lupus vulgaris lesion, 315

Cook, S D: *see* Menage, M J, etc, 532
Corridan, P, Nightingale, S, Mashoudi, N, Williams, A C: Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm, 309
de Courten, C: *see* BenEzra, D, etc, 350
Cox, S N: *see* Lau, R K W, etc, 52
de Crecchio, G: *see* Cannamo, G, etc, 700
Crick, R P: *see* Vogel, R, etc, 3
Crossman, J. L: *see* Mainster, M A, etc, 177
Cunningham, C: *see* Rosenblatt, M A, etc, 610

Dabbs, T R, Skjodt, K: Prevalence of angioid streaks and other ocular complications of Paget's disease of bone, 579
Dallas, N L: *see* Redmond, R M, etc, 203
Dally, S: *see* Ingram, R M, etc, 82, 158
Damji, K F: *see* Antle, C M, etc, 502
Dark, A J, Streeten, B W: Precapsular film on the aging human lens: precursor of pseudoexfoliation? 717
Darougar, S: *see* Babalola, O E, etc, 89
Dart, J (*Editorial*): Contamination of contact lens storage cases, 129
Darville, J M: *see* Menage, M J, etc, 532
David, R, Tessler, Z, Yagev, R, Briscoe, D, Biedner, B Z, Gilad, E, Yassur, Y: Persistently raised intraocular pressure following extracapsular cataract extraction, 272
Decker, W L: *see* Maguire, J I, etc, 556
Deger, O: *see* Akyol, N, etc, 661
De Rosa, J T: *see* Spaide, R F, etc, 536
Dick, A D, Jagger, J, McCartney, A C E: Refsum's disease: electron microscopy of an iris biopsy, 370
Dickinson, A J, Rosenthal, A R, Nicholson, K G: Inflammation of the retinal pigment epithelium: a unique presentation of ocular schistosomiasis, 440
Di Loreto, D A, Kennedy, R A, Neigel, J M, Rootman, J: Infestation of extraocular muscle by *Cysticercus cellulosae*, 751
De Doncker, R M L, de Keizer, R J W, Oosterhuis, J A, Maes, A: Scleral melting in a patient with conjunctival rhinosporidiosis, 635
Douglas, G R: *see* Schulzer, M, etc, 196
Dowd, T C: *see* Kaye, S B, etc, 114
Drance, S M: *see* Schulzer, M, etc, 196
Dunn, D T: *see* Fox, P D, etc, 172
Dunne, J A: *see* Prasad, P, etc, 313
Dutton, G N: *see* Teoh, Su Lin, etc, 215
——: *see* Zeki, S M, etc, 300

Easty, D L: *see* Armitage, W J, etc, 685
——: *see* Larkin, D F P, etc, 133, 551
——: *see* Menage, M J, etc, 532
——: *see* Ragge, N K, etc, 561
——: *see* Tarlton, J F, etc, 144
Easty, V S: *see* Menage, M J, etc, 532
Edip Keha, E: *see* Akyol, N, etc, 661
Eliason, J A, Maurice, D M: Staining of the conjunctiva and conjunctival tear film, 519
Erdey, R A: *see* Finger, P R, etc, 121
Erickson, P J: *see* Mainster, M A, etc, 177
Esakowitz, L: *see* Winfield, A J, etc, 477
Estreich, S: *see* Lau, R K W, etc, 52

Falcão-Reis, F, O'Donoghue, E, Buceti, R, Hitchings, R A, Arden, G B: Peripheral contrast sensitivity in glaucoma and ocular hypertension, 712
Farrington, M: *see* Barker, C, etc, 247
Fass, D: *see* Abramson, D H, etc, 359
Feldon, S E, Levin L: Graves' ophthalmopathy. V. Aetiology of upper eyelid retraction in Graves' ophthalmopathy, 484
Fells, P: *see* Morris, R J, etc, 490
Ferrer, J: *see* Backon, J, etc, 607
ffytche, T J: *see* McHugh, D, etc, 743
Fielder, A R: *see* Robinson, J, etc, 64
Finger, P T, Perry, H D, Packer, S, Erdey, R A, Weisman, G D, Sibony, P A: Posterior scleritis as an intraocular tumour, 121
——: *see* Stroh, E M, etc, 380
Fink, B A, Hill, R M, Carney, L G: Corneal oxygenation: blink frequency as a variable in rigid contract lens wear, 168
Finkelstein, I, Trope, G E, Basu, P K, Hasany, S M, Hunter, W S: Quantitative analysis of collagen content and amino acids in trabecular meshwork, 280
Firth, A Y: Pupillary responses in amblyopia, 676
Fischer, D H: *see* Maguire, J I, etc, 556
Fitzke, F W: *see* Meyer, P A R, etc, 275
——: *see* Tuft, S J, etc, 78
Fleck, B W: How large must an iridotomy be? 583
Fleming, J: *see* Rimmer, T, etc, 400
Forrester, J: *see* Singh, A, etc, 328
Forrester, J V: Endogenous posterior uveitis, 620
Foster, C S: *see* Hemady, R, etc, 26
Foulds, W S: Management of intraocular melanoma, 559
——: *see* Teoh, Su Lin, etc, 215
Fox, P D, Acheson, R W, Serjeant, G R: Outcome of iatrogenic choroidal neovascularisation in sickle cell disease, 417
——, **Dunn, D T, Morris, J S, Serjeant, G R**: Risk factors for proliferative sickle retinopathy, 172
Frangoulis, M A: *see* Goble, R R, etc, 574
Friedman, A H: *see* Brodie, S E, etc, 49
Frith, P, Burge, S M, Millard, P R, Wojnarowska, F: External ocular findings in lupus erythematosus: a clinical and immunopathological study, 163
Fuhrmann, P: *see* Lommatzsch, P K, etc, 615
Fujiwara, H, Takigawa, Y, Ueno, S, Okuda, K: Histology of the lens in Weill-Marchesani syndrome, 631
Fukuda, M: *see* Saito, Y, etc, 702
Furuse, N, Hayasaka, S, Yamamoto, Y, Setogawa, T: Corneal endothelial changes after posterior chamber intraocular lens implantation in patients with or without diabetes mellitus, 258

Gaal, J: *see* Singh, A, etc, 328
Gagné, R: *see* Jotterand, V, etc, 568
Gardner, I D: *see* Hykin, P G, etc, 499
Garner, A (*Editorial*): Exfoliation syndrome, 449
——: Some recent developments in ophthalmic pathology, 186
Garus, H: *see* Pfeiffer, N, etc, 405
Gelfand, Y: *see* Carmichael, T R, etc, 528
Geyer, O, Rothkoff, L, Lazar, M (*Correspondence*): Malignant glaucoma after laser iridotomy: *see* 576
——, **Wasserman, D, Rothkoff, L, Lazar, M**: Orbital haemorrhage induced by labour, 242
Gibson, J M: *see* Hansel, T T, etc, 118
Gilad, E: *see* David, R, etc, 272
Gillies, W E: *see* Brooks, A M V, etc, 576
Giuliano, M: *see* Midena, E, etc, 106
Goble, R R, Frangoulis, M A: Lymphangioma circumscription of the eyelids and conjunctiva, 574
——, **McKenzie, J, Kingston, J E, Plowman, P N, Hungerford, J L**: Orbital recurrences of retinoblastoma successfully treated by combined therapy, 97
Goh, B T: *see* Lau, R K W, etc, 52
Goldberg, B B: *see* Lieb, W E, etc, 305
Gormus, B J: *see* Hussein, N, etc, 647
Goulstine, D B: *see* Wang Yu-dong, etc, 650
Gray, J J: *see* Charles, S J, etc, 286
Gray, P J (*Correspondence*): More Healonid for your money, 384
Gray, R (*Correspondence*): Chart for visual acuity screening, 125
Grayson, M C: *see* Mackintosh, G I S, etc, 748
Green, S N: *see* Leff, S R, etc, 498
Grehn, F: *see* Pfeiffer, N, etc, 405
Gremillion, C M Jr, Peyman, G A, Liu, K-R, Naguib, K S: Fluorosilicone oil in the treatment of retinal detachment, 643
Grierson, I: *see* Morino, I, etc, 393
Griffith, G A P, Marsh, I B, Ridgway, A E A (*Correspondence*): Treatment of developmental glaucoma, 384
Grochowicki, M, Vighetto, A, Berquet, S, Sassolas, G: Contrast sensitivity function and pituitary adenoma: a study of 40 cases, 358
Gronemeyer, U: *see* Lieb, W, etc, 59
Gupta, A: *see* Mohan, K, etc, 311
Guy, J: *see* O'Brien, W J, etc, 723

Hainsworth, M: *see* Cook, C D, etc, 315
Hakin, K N, Yokoyama, C, Wright, J E: Hemifacial atrophy: an unusual cause of enophthalmos, 496
Halliday, B L: Epikeratophakia for aphakia, keratoconus, and myopia, 67
——, **Ritten, S A**: Effect of donor parameters on primary graft failure and the recovery of acuity after keratoplasty, 7
Hamilton, P A M: *see* McHugh, D, etc, 743
Hansel, T T, O'Neill, D P, Yee, M L, Gibson, J M, Thompson, R A: Infective conjunctivitis and corneal scarring in three brothers with sex linked hypogammaglobulinaemia (Bruton's disease), 118
Hansen, L L: *see* Wiek, J, etc, 665
Hardman Lea, S J, Rubinstein, M P, Snead, M P, Haworth, S M: Pseudophakic accommodation? A study of the stability of capsular bag supported, one piece, rigid tripod, or soft flexible implants, 22
Harnois, C: *see* Jotterand, V, etc, 568
Harper, C A: *see* Brooks, A M V, etc, 576
Harrie, R: *see* Char, D H, etc, 183
Hart, C A: *see* Kaye, S B, etc, 114
Hart, J C D: *see* Ragge, N K, etc, 561
Hasany, S M: *see* Finkelstein, I, etc, 280
Haworth, S M: *see* Hardman Lea, S J, etc, 22
Hayasaka, S: *see* Furuse, N, etc, 258
Heacock, G L: *see* Mainster, M A, etc, 177
Hemady, R, Zaltas, M, Paton, B, Foster, C S, Baker, A S: *Bacillus*-induced endophthalmitis: new series of 10 cases and review of the literature, 26
Hendrix, L: *see* Williams, D F, etc, 43
Hennekes, R: *see* Pfeiffer, N, etc, 405

Henry, D J: *see* Vernon, S A, etc, 220
Hessburg, P C (*Correspondence*): Mollicute-like organisms, 447
Hidayat, A: *see* Al-haddab, S, etc, 123
Hill, R M: *see* Fink, B A, etc, 168
Hing, S, Speedwell, L, Taylor, D: Lens surgery in infancy and childhood, 73
Hirsh, A, Alhalel, A, Weiss, A, Breuer, H, Avni, I: Bilateral total corneal epithelial erosion as a side-effect of cytotoxic therapy, 638
Hiscott, P: *see* Morino, I, etc, 393
Hitchings, R A: *see* Falcão-Reis, F, etc, 712
Holland, G N: *see* Panek, W C, etc, 223
Holmes, J: *see* Morsman, C D G, etc, 563
Hommura, S: *see* Ishibashi, Y, etc, 433
Hon Liu, J: *see* Yung Yen, M, etc, 188
Horiuchi, T: *see* Shiono, T, etc, 317
Huber, M J E: *see* Reacher, M H, etc, 109
Hungerford, J (*Editorial*): Histogenesis of retinoblastoma, 131
——: *see* Rahi, J, etc, 377
——: *see* Shine, B S F, etc, 427
Hungerford, J L: *see* Goble, R R, etc, 97
——. *see* Hykin, P G, etc, 36
Hunter, J V, Yokoyama, C, Moseley, I F, Wright, J E: Aneurysmal bone cyst of the sphenoid with orbital involvement, 505
Hunter, W S: *see* Finkelstein, I, etc, 280
Hussein, N, Ostler, B, Gormus, B J, Wolf, R, Walsh, G P: Intraocular pressure changes and postural changes of intraocular pressure in experimentally induced Hansen's disease of rhesus, mangabey, and African green monkeys, 647
Hykin, P G, Gardner, I D, Wheatcroft, S M: Optic nerve avulsion due to forced rotation of the globe by a snooker cue, 499
——, **McCartney, A C E, Plowman, P N, Hungerford, J L:** Postenucleation orbital radiotherapy for the treatment of malignant melanoma of the choroid with extrascleral extension, 36

Iaccarino, G: *see* Cannamo, G, etc, 700
Ibechukwu, B I: Simultaneous pterygium and intraocular surgery, 265
Ilsar, M: *see* Pe'er, J, etc, 624
Ingram, R M, Arnold, P E, Dally, S, Lucas, J: Results of a randomised trial of treating abnormal hypermetropia from the age of 6 months, 158
——, **Walker, C, Billingham, B, Lucas, J, Dally, S:** Factors relating to visual
acuity in children who have been treated for convergent squint, 82
Ishibashi, Y, Watanabe, R, Hommura, S, Koyama, A, Ishikawa, T, Mikami, Y: Endogenous *Nocardia asteroides* endophthalmitis in a patient with systemic lupus erythematosus, 433
Ishikawa, S: *see* Mezawa, M, etc, 472
Ishikawa, T: *see* Ishibashi, Y, etc, 433

Jaffe, G J: *see* Williams, D F, etc, 43
Jager, M J: *see* Schaling, D F, etc, 538
Jagger, J: *see* Dick, A D, etc, 370
Jalali, S: *see* Mohan, K, etc, 311
Jay, B: New light on visual pigment genes, 238
Jay, J L: *see* Pitts, J F, etc, 601
Jenkins, C D G, McDonnell, P J, Spalton, D J: Randomised single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery, 734
Jenkins, P: *see* Oster, J G, etc, 709
Jenkins, T C A, Cartwright, J P: The electroretinogram in minimal diabetic retinopathy, 681
Jennings, T: *see* Tessler, H H, etc, 353
Jessiman, D: *see* Winfield, A J, etc, 477
Ji Jaw, S: *see* Yung Yen, M, etc, 188
Johnson, A: *see* Stayte, M, etc, 465
Jones, N P: Self-enucleation and psychosis, 571
Jones, S J: *see* Vernon, S A, etc, 220
Joshi, K: *see* Mohan, K, etc, 311
Jotterand, V, Boisjoly, H M, Harnois, C, Bigonesse, P, Laframboise, R, Gagné, R, St Pierre, A: 11p 13 Deletion, Wilms' tumour, and aniridia: unusual genetic, non-ocular and ocular features in three cases, 568
Joyce, P W, Mills, K B: Comparison of the effect of acetazolamide tablets and Sustets on diurnal intraocular pressure in patients with chronic simple glaucoma, 413

Katz, B, Melles, R B, Swenson, M R, Schneider, J A: Photic sneeze reflex in nephropathic cystinosis, 706
——, **Weinreb, R N, Wheeler, D T, Klauber, M R:** Anterior ischaemic optic neuropathy and intraocular pressure, 99
Kauffmann, D J H, Wormser, G P: Ocular Lyme disease: case report and review of the literature, 325
Kaye, S B, Madan, N, Dowd, T C, Hart, C A, McCarthy, K, Patterson, A: Ocular shedding of herpes simplex virus, 114
——: *see* Wong, D, etc, 125
de Keizer, R J W: *see* De Doncker, R M L, etc, 635
——: *see* de Vries, J, etc, 344
Kellen, R I, Schrank, B, Burde, R M: Yellow forelock – a new neuro-ophthalmological sign, 509
Kelly, S P, Rosenthal, A R: Chickenpox chorioretinitis, 698
Kennedy, R A: *see* Di Loreto, D A, etc, 751
Kerman, B: *see* Char, D H, etc, 183
Kerr-Muir, M G, O'Sullivan G (*Correspondence*): Local anaesthesia for cataract surgery, 639
Khaw, P T, Lavin, M J (*Correspondence*): Viscoelastic agents in ocular surgery, 512
——: *see* Lavin, M J, etc, 192
Kho, P: *see* Porter, S M, etc, 283
Khoo, C Y (*Correspondence*). Local anaesthesia without retrobulbar injection, 639
Kijlstra, A: *see* de Vries, J, etc, 344
Kilic, S: *see* Akyol, N, etc, 661
Kilvington, S: *see* Larkin, D F P, etc, 133
Kingston, J E: *see* Goble, R R, etc, 97
Kinsella, F, Kyle, P, Stansfield, A: Bilateral failure of adduction following orbital decompression, 239
Kirsch, I: *see* Lommatzsch, P K, etc, 615
Klauber, M R: *see* Katz, B, etc, 99
Klinge, B: *see* Behrens-Baumann, W, etc, 40
Kohner, E M: *see* Rimmer, T, etc, 400
Konstas, A G, Marshall, G E, Lee, W R: Immunogold localisation of laminin in normal and exfoliative iris, 450
——: *see* Marshall, G E, etc, 228
Koorneef, L: *see* Mourits, M Ph, etc, 481
——: *see* Suttorp-Schulten, M S A, etc, 694
Koyama, A: *see* Ishibashi, Y, etc, 433
Koyama, M: *see* Matsuo, T, etc, 443
Kriss, A: *see* Russell-Eggitt, I, etc, 136
Kroll, S: *see* Char, D H, etc, 183
van Kroonenburgh, M J P G: *see* Schaling, D F, etc, 538
Kwok, L S (*Correspondence*): Measurement of corneal diameter, 63
Kyle, P: *see* Kinsella, F, etc, 239

Laframboise, R: *see* Jotterand, V, etc, 568
Lai, Y-K: Treatment of macular hole retinal detachment, 201
Laker, M F: *see* McKenna, P, etc, 629
Lane, C: *see* Singh, A, etc, 328
Larkin, D F P, Easty, D L: Experimental *Acanthamoeba* keratitis I. Preliminary findings, 551
——, **Kilvington, S, Easty, D L:** Contamination of contact lens storage cases by *Acanthamoeba* and bacteria, 133
Lau, R K W, Goh, B T, Estreich, S, Cox, S N, Levy I: Adult gonococcal keratoconjunctivitis with AIDS, 52
Lau, W: *see* Schulzer, M, etc, 196
Lavin, M J, Khaw, P T (*Correspondence*): Use of viscoelastic agents to aid visualisation during ocular surgery, 192
——, *see* **Khaw, P T**, etc, 512
Lawrenson, J: *see* Tuft, S J, etc, 78
Lazar, M: *see* Geyer, O, etc, 242, 576
Lee, D E: *see* Panek, W C, etc, 223
Lee, N B: Biomicroscopic examination of the ocular fundus with a +150 dioptre lens, 294
Lee, W R: *see* Charteris, D G, etc, 688
——: *see* Konstas, A G, etc, 450
——. *see* Marshall, G E, etc, 228
Leff, S R, Yarian, D L, Masciulli, L, Green, S N, Baldomero, R E: Vitreous haemorrhage as a complication of HELLP syndrome, 498
Leitch, J: *see* Barker, C, etc, 247
Leitch, R J, Burke, J P, Strachan, I M: Convergence excess esotropia treated surgically with fadenoperation and medial rectus muscle recessions, 278
Levin, L: *see* Feldon, S E, etc, 484
Levinger, S: *see* Pe'er, J, etc, 624
Levy, A M: *see* Sunder Raj, P, etc, 731
Levy, I: *see* Lau, R K W, etc, 52
Lieb, W, Rochels, R, Gronemeyer, U: Microphthalmos with colobamatous orbital cyst: clinical, histological, immunohistological and electron microscopic findings, 59
Lieb, W E, Merton, D A, Shields, J A, Cohen, S M, Mitchell, D D, Goldberg, B B: Colour Doppler imaging in the demonstration of an orbital varix, 305
——, **Shields, J A, Shields, C L, Spaeth, G L:** Mucinous adenocarcinoma metastatic to the iris, ciliary body, and choroid, 373
Lieberman, R M: *see* Orellana, J, etc, 511
van Lierde, A: *see* Menage, M J, etc, 532
Liguori, G: *see* Cennamo, G, etc, 700
Lippa, E A: *see* Pfeiffer, N, etc, 405
Liu, K-R: *see* Gremillion, C M Jr, etc, 643
Loewenthal, R, Pe'er, J: A prevalence survey of ophthalmic diseases among the Turkana tribe in north-west Kenya, 84
Lommatzsch, P K, Lommatzsch, R E, Kirsch, I, Fahrmann, P: Therapeutic outcome of patients suffering from malignant melanomas of the conjunctiva, 615
Lommatzsch, R E: *see* Lommatzsch, P K, etc, 615

Longstaff, S: *see* West, J, etc, 663
Lucas, J: *see* Ingram, R M, etc, 82, 158
Lund-Andersen, H: *see* Bek, T, etc, 388

McCarthy, K: *see* Kaye, S B, etc, 114
McCartney, A C E: *see* Dick, A D, etc, 370
——: *see* Hykin, P G, etc, 36
McCormick, B: *see* Abramson, D H, etc, 359
McDonnell, P J: *see* Jenkins, C D G, etc, 734
McHugh, D, Marshall, J, ffytche, T J, Hamilton, P A M, Raven, A: Diode laser trabeculoplasty (CD7) for primary open-angle glaucoma and ocular hypertension, 743
McKechnie, N: *see* Morino, I, etc, 393
McKenna, P, Morgan, S J, Bosanquet, R C, Laker, M F: A case of cerebrotendinous xanthomatosis. II: The sterol content of a cataractous lens, 629
McKenzie, J: *see* Goble, R R, etc, 97
Mackintosh, G I S, Grayson, M C: Atraumatic iris cilia, 748
McLeod, D: *see* Singh, A, etc, 328
McNab, A A, Mosley, O: Primary orbital liposarcoma: clinical and computed tomographic features, 437
Madan, N: *see* Kaye, S B, etc, 114
Maes, A: *see* De Doncker, R M L, etc, 635
Maftzir, G: *see* Benezra, D, etc, 350
Maggi, C, Maggi, R: Artificial maintenance of the relative ocular tissue pressure during eye surgery, 462
Maggi, R: *see* Maggi, C, etc, 462
Maguire, J I, Annesley, W H Jr, Decker, W L, Brown, G C, Fischer, D H, Slagle, J M: Computerised visual field deficits in tears of the retinal pigment epithelium, 556
Mainster, M A, Crossman, J L, Erickson, P J, Heacock, G L: Retinal laser lenses: magnification, spot prize and field of view, 177
——: *see* Whitacre, M M, etc, 233
Manoukian, N: *see* Whitacre, M M, etc, 233
Manschot, W A: Morning glory syndrome: a histopathological study, 56
Marmor, M F: Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function, 739
Marsh, I B: *see* Griffith, G A P, etc, 384
Marshall, G E, Konstas, A G, Lee, W R: Ultrastructural distribution of collagen types I-VI in aging human retinal vessels, 228
——: *see* Konstas, A G, etc, 450
Marshall, J: *see* McHugh, D, etc, 743
——: *see* Tuft, S J, etc, 78
Masciulli, L: *see* Leff, S R, etc, 498
Mashoudi, N: *see* Corridan, P, etc, 309
Matamoros, N: *see* Backon, J, etc, 607
Matsuo, N: *see* Matsuo, T, etc, 443
Matsuo, T, Koyama, M, Matsuo, N: Acute retinal necrosis as a novel complication of chickenpox in adults, 443
Matthews, J C: *see* Clarke, M P, etc, 526
Maudgal, P C: Cytopathology of adenovirus keratitis by replica technique, 670
Maurice, D M: *see* Eliason, J A, etc, 519
Mehra, V: *see* Minassian, D C, etc, 341
Melles, R B: *see* Katz, B, etc, 706
Menage, M J, de Clercq, E, van Lierde, A, Easty, V S, Darville, J M, Cook, S D, Easty, D L: Antiviral drug sensitivity in ocular herpes simplex virus infection, 532
Merton, D A: *see* Lieb, W E, etc, 305
van der Meulen-Schot, H M: *see* Mourits, M Ph, etc, 481
Meyer, P A R, Fitzke, F E: Computer assisted analysis of fluorescein videoangiograms, 275
Mezawa, M, Ishikawa, S, Ukai, K: Changes in waveform of congenital nystagmus associated with biofeedback treatment, 472
Midena, E, Segato, T, Giuliano, M, Zuccheto, M: Macular recovery function (nyctometry) in diabetics without and with early retinopathy, 106
Mieler, W F: *see* Williams, D F, etc, 43
Mikami, Y: *see* Ishibashi, Y, etc, 433
Millard, P R: *see* Frith, P, etc, 163
Mills, K B: *see* Joyce, P W, etc, 413
Minassian, D C, Mehra, V: 3.8 Million blinded by cataract each year: projections from the first epidemiological study of incidence of cataract blindness in India, 341
——: *see* Barondes, M, etc, 180
Mitchell, D D: *see* Lieb, W E, etc, 305
Mohan, K, Gupta, A, Saini, J S, Jalali, S, Joshi, K: Retinoblastoma metastatic to the contralateral orbit, 311
Morgan, S J: *see* McKenna, P, etc, 629
Morino, I, Hiscott, P, McKechnie, N, Grierson, I: Variation in epiretinal membrane components with clinical duration of the proliferative tissue, 393
Morris, J S: *see* Fox, P D, etc, 172
Morris, R J, Rosen, P H, Fells, P: Incidence of inadvertent globe perforation during strabismus surgery, 490
Morsman, C D G, Holmes, J: Traumatic hyphaema in a haemophiliac, 563
Moseley, I: Diagnostic value of 'optic foramen views': experience from an eye hospital, 235
——: *see* McNab, A A, etc, 437
Moseley, I F: *see* Hunter, J V, etc, 505
Moss, S J: *see* Armitage, W J, etc, 685
van Mourik-Noordenbos, A M: *see* Mourits, M Ph, etc, 481
Mourits, M Ph, Koorneef, L, van Mourik-Noordenbos, A M, van der Meulen-Schot, H M, Prummel, M F, Wiersinga, W M, Berghout, A: Extraocular muscle surgery for Graves' ophthalmopathy: does prior treatment influence surgical outcome? 481

Naguib, K S: *see* Gremillion, C M Jr, etc, 643
Nartey, I N, Sherrard, E S, Ng, W (*Correspondence*): Amitosis in human donor corneal endothelium – a serendipity? 63
——, **Sherrard, E S, Steele, A D McG:** Manipulative damage to the endothelium of infant and adult donor corneas, 261
Neigel, J M: *see* DiLoreto, D A, etc, 751
Neil, H A W: *see* Sparrow, J M, etc, 654
Nelson, L B: *see* Smoot, C N, etc, 155
Nelson, M E: *see* Benson, M T, etc, 103
Newson, R B: *see* Vogel, R, etc, 3
Ng, W: *see* Nartey, I N, etc, 63
Nicholson, K G: *see* Dickinson, A J, etc, 440
Nightingale, S: *see* Corridan, P, etc, 309
Norrsell, K: *see* Aurell, E, etc, 589

O'Brien, W J, Guy, J, Taylor, J L: Pathogenesis of corneal oedema associated with herpetic eye disease, 723
O'Connor, G M, Thiru, A A A, Caul, O E: Ocular cowpox: transmission from the domestic cat to man, 245
O'Donoghue, E: *see* Falcão-Reis, F, etc, 712
Okon, E: *see* Pe'er, J, etc, 624
Okuda, K: *see* Fujiwara, H, etc, 631
Omoto, T: *see* Saito, Y, etc, 702
O'Neill, D P: *see* Hansel, T T, etc, 118
Oosterhuis, J A: *see* De Doncker, R M L, etc, 635
——: *see* Schaling, D F, etc, 254, 538
Orellana, J, Lieberman, R M, Peairs, R, Restreppo, S (*Correspondence*): Intravitreal therapy with ganciclovir for posterior pole cytomegalovirus retinitis in AIDS patients, 511
O'Riordan, M (*Correspondence*): Compact field charts, 704
O'Riordan, M D: Trial frame for children, 639
Oster, J G, Simon, J W, Jenkins, P: When is it safe to stop patching? 709
Ostler, B: *see* Hussein, N, etc, 647
O'Sullivan, G: *see* Kerr-Muir, M G, etc, 639

Packer, S: *see* Finger, P T, etc, 121
Panek, W C, Holland, G N, Lee, D E, Christensen, R E: Glaucoma in patients with uveitis, 223
Paton, B: *see* Hemady, R, etc, 26
Patterson, A: *see* Atkinson, P L, etc, 750
——: *see* Kaye, S B, etc, 114
——: *see* Porter, S M, etc, 283
Pauleikhoff, D: *see* Barondes, M, etc, 180
Pauwels, E: *see* Schaling, D F, etc, 254
Peairs, R: *see* Orellana, J, etc, 511
Pearce, J L: *see* Searle, A E T, etc, 19
Pearson, J C G: *see* Clarke, M P, etc, 526
Pe'er, J, Levinger, S, Ilsar, M, Climenhaga, H, Okon, E: Malignant fibrous histiocytoma of the conjunctiva, 624
——: *see* Loewenthal, R, 84
Perry, H D: *see* Finger, P T, etc, 121
Peyman, G A: *see* Gremillion, C M Jr, etc, 643
Pfeiffer, N, Hennekes, R, Lippa, E A, Grehn, F, Garus, H, Brunner-Ferber, F L: A single dose of the topical carbonic anhydrase inhibitor MK-927 decreases IOP in patients, 405
Phelps Brown, N A: *see* Sparrow, J M, etc, 654
Phillips, C I: Aetiology of myopia, 47
Pitts, J F, Jay, J L: The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma, 601
Plowman, P N: *see* Goble, R R, etc, 97
——: *see* Hykin, P G, etc, 36
van der Pol, J P: *see* Schaling, D F, etc, 538
Porter, S M, Patterson, A, Kho, P: A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis, 283
Pradhan, H: *see* Brandt, F, etc, 14
Prasad, P, Setna, P H, Dunne, J A: Accelerated ocular neovascularisation in diabetics following posterior chamber lens implantation, 313
Prummel, M F: *see* Mourits, M Ph, etc, 481

Ragge, N K, Hart, J C D, Easty, D L, Tyers, A G: A case of fungal keratitis caused by *Scopulariopsis brevicaulis*: treatment with antifungal agents and penetrating keratoplasty, 561
Rahi, J, Hungerford, J: Early diagnosis of the retinopathy of incontinentia pigmenti: successful treatment by cryotherapy, 377
Rai, N: *see* Brandt, F, etc, 14

Raitta, C, Carlson, S, Vannas-Sulonen, K: Gyrate atrophy of the choroid and retina: ERG of the neural retina and the pigment epithelium, 363

Ramirez, M: *see* Backon, J, etc, 607

Ratcliffe, P: *see* Shun-Shin, G A, etc, 267

Raven, A: *see* McHugh, D, etc, 743

Reacher, M H, Huber, M J E, Canagaratnam, R, Alghassany, A: A trial of surgery for trichiasis of the upper lid from trachoma, 109

Redmond, R M (*Correspondence*): Local anaesthesia without retrobulbar injection, 639

——, **Dallas, N L:** Extracapsular cataract extraction under local anaesthesia without retrobulbar injection, 203

Refaat, R F, Allan, D (*Correspondence*): Optimal surface for impression cytology, 254

Rennie, I: *see* Benson, M T, etc, 251

Restreppo, S: *see* Orellana, J, etc, 511

Richardson, J: *see* Chowdhury, C R, etc, 445

——: *see* Wood, C M, etc, 93, 208

Ridgway, A E A: *see* Griffith, G A P, etc, 384

Rimmer, T, Fleming, J, Kohner, E M: Hypoxic viscosity and diabetic retinopathy, 400

Ritten, S A: *see* Halliday, B L, etc, 7

Robertson, D M: *see* Williams, D F, etc, 43

Robinson, J, Fielder, A R (*Correspondence*): Measurement of corneal diameter, 64

Rochels, R: *see* Lieb, W, etc, 59

Roper-Hall, M J: Anterior segment surgery, 368

Rootman, J: *see* Antle, C M, etc, 502

——: *see* Di Loreto, D A, etc, 751

Rose, G E, Billington, B M, Chignell, A H: Immunoglobulins in paired specimens of vitreous and subretinal fluids from patients with rhegmatogenous retinal detachment, 160

——, **Sigurdsson, H, Collin, R:** The volume-deficient orbit: clinical characteristics, surgical management, and results after extraperiorbital implantation of silastic block, 545

Rosen, E S: *see* Watson, A P, etc, 458

Rosen, N: *see* Ashkenazi, I, etc, 254

Rosen, P H: *see* Morris, R J, etc, 490

Rosenblatt, M A, Cunningham, C, Teich, S, Friedman, A H: Choroidal lesions in patients with AIDS, 610

Rosenthal, A R: *see* Dickinson, A J, etc, 440

——: *see* Kelly, S P, etc, 698

——: *see* Wang Yu-dong, etc, 650

Ross-Degnan, D: *see* Whitfield, R, etc, 333

Rostron, C (*Correspondence*): Epikeratophakia with biological adhesive, 384

Roth, J A (*Correspondence*): Diabetes and retinal function, 704

Rothkoff, L: *see* Geyer, O, etc, 242, 576

Rothova, A: *see* de Vries, J, etc, 344

Rubinstein, M P: *see* Hardman Lea, S J, etc, 22

Ruchel, R: *see* Behrens-Baumann, W, etc, 40

Ruiter, D J: *see* Schaling, D F, etc, 538

Russell-Eggitt, I, Kriss, A, Taylor, D S I: Albinism in childhood: a flash VEP and ERG study, 136

Russell-Eggit, I M, Blake, K D, Taylor, D S I, Weyse, R K H: The eye in the CHARGE association, 421

Saini, J S: *see* Mohan, K, etc, 311

St Pierre, A: *see* Jotterand, V, etc, 568

Saito, Y, Omoto, T, Fukuda, M: Lobular pattern of choriocapillaris in pre-eclampsia with aldosteronism, 702

Salu, P, Stempels, N, Vanden Houte, K, Verbeelen, D: Acute tubulo-interstitial nephritis and uveitis syndrome in the elderly, 53

Samaila, E: *see* Babalola, O E, etc, 89

Samuel, P R: *see* Chowdhury, C R, etc, 445

Sanchez, R M: *see* Backon, J, etc, 607

Sanders, M D: Neuro-ophthalmology, 494

Sassolas, G: *see* Grochowicki, M, etc, 358

Saunders, D C: Acute closed-angle glaucoma and Nd-YAG laser iridotomy, 523

Schade, M: *see* Wiek, J, etc, 665

Schaling, D F, Oosterhuis, J A, Pauwels, E (*Correspondence*): Ocular melanoma, 254

——, **van der Pol, J P, Jager, M J, van Kroonenburgh, M J P G, Oosterhuis, J A, Ruiter, D J:** Radio-immunoscintigraphy and immunohistochemistry with melanoma-associated monoclonal antibodies in choroidal melanoma: a comparison of the clinical and immunohistochemical results, 538

Schneider, J A: *see* Katz, B, etc, 706

Schrank, B: *see* Kellen, R I, etc, 509

Schulzer, M, Drance, S M, Carter, C J, Brooks, D E, Douglas, G R, Lau, W: Biostatistical evidence for two distinct chronic open angle glaucoma populations, 196

Schwab, L: *see* Whitfield, R, etc, 333

Schweitzer, C M C: *see* de Vries, J, etc, 344

Scott, J D: Fluorosilicone oil for retinal detachment, 641

Searle, A E T, Pearce, J L, Shaw, D E: Topical use of indomethacin on the day of cataract surgery, 19

Segato, T: *see* Midena, E, etc, 106

Serjeant, G R: *see* Fox, P D, etc, 172, 417

Servodidio, C A: *see* Abramson, D H, etc, 359

Setna, P H: *see* Prasad, P, etc, 313

Setogawa, T: *see* Furuse, N, etc, 258

Shaw, D E: *see* Searle, A E T, etc, 19

Sheraidah, G A K: *see* Shine, B S F, etc, 427

Sherrard, E S: *see* Nartey, I N, etc, 63, 261

Shi, Z R: *see* Brandt, F, etc, 14

Shields, C L: *see* Lieb, W E, etc, 373

Shields, J A: *see* Lieb, W E, etc, 305, 373

Shine, B S F, Hungerford, J, Vaghela, B, Sheraidah, G A K: Electrophoretic assessment of aqueous and serum neurone-specific enolase in retinoblastoma and ocular malignant melanoma, 427

Shiono, T, Abe, S, Horiuchi, T: A case of miliary tuberculosis with disseminated choroidal haemorrhages, 317

Shipley, M: *see* Vogel, R, etc, 3

Shun-Shin, G A, Ratcliffe, P, Bron, A J, Brown, N P, Sparrow, J M: The lens after renal transplantation, 267

——: *see* Smith, G T H, etc, 564

Sibony, P A: *see* Finger, P T, etc, 121

Sigardsson, H: *see* Rose, G E, etc, 545

Silver, J: *see* Tuft, S J, etc, 78

Simon, J W: *see* Oster, J G, etc, 709

——: *see* Smoot, C N, etc, 155

Singh, A, Boulton, M, Lane, C, Forrester, J, Gaal, J, McLeod, D: Inhibition of microvascular endothelial cell proliferation by vitreous following retinal scatter photocoagulation, 328

Skerry, J E: *see* Spaide, R F, etc, 536

Skjodt, K: *see* Dabbs, T R, etc, 579

Slagle, J M: *see* Maguire, J I, etc, 556

Smith, D A, Trope, G E: Effect of a β-blocker on altered body position: induced ocular hypertension, 605

Smith, G T A, Shun-Shin, G A, Boon, A: Spontaneous resorption of a rubella cataract, 564

Smith, R (*Editorial*): Albinism and anatomy, 130

————: Are there two varieties of primary open-angle glaucoma? 193

————: Cararact extraction without retrobulbar anaesthetic injection, 205

————: Diabetes and retinal function, 385

————: Diabetic retinopathy: a new clue in the puzzle, 387

————: Getting an air lock on the macular hole, 194

————: Glaucoma: is there light at the end of the tunnel? 1

————: How safe are intraocular lenses? 257

————: Lye in the eye, 513

————: Natural history of epiretinal membranes, 386

————: Neovascularisation again, 323

————: Not enough cataract surgeons, 324

————: Paediatric cataract surgery, 66

————: Paget's disease and angioid streaks: one complication less? 577

————: Photic sneezes, 705

————: The BJO in the 1990s, 1

————: The living contact lens, 65

Smoot, C N, Simon, J W, Nelson, L B: Binocularity following surgery for secondary esotropia in childhood, 155

Snead, M P: *see* Hardman Lea, S J, etc, 22

Spaeth, G L: *see* Lieb, W E, etc, 373

Spaide, R F, Ward, D L: Conjunctival biopsy in the diagnosis of sarcoidosis, 465

——, **Skerry, J E, Yannuzzi, L A, DeRosa, J T:** Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis, 536

Spalton, D J (*Editorial*): Lyme disease, 321

——: Ocular fluorophotometry, 431

——: *see* Jenkins, C D G, etc, 734

——: *see* Walters, R F, etc, 30

——: *see* Wood, W H, etc, 212

Sparrow, J M, Bron, A J, Phelps Brown, N A, Neil, H A W: Biometry of the crystalline lens in early-onset diabetes, 654

——: *see* Shun-Shin, G A, etc, 267

Speedwell, L: *see* Amaya, L G, etc, 150

——: *see* Hing, S, etc, 73

Stansfield, A: *see* Kinsella, F, etc, 239

Stayte, M, Johnson, A, Wortham, C: Ocular and visual defects in a geographically defined population of 2-year-old children, 465

Steele, A (*Editorial*): Cataract surgery, 130

————: —— Local anaesthesia for cataract surgery, 195

Steele, A D McG: *see* Nartey, I N, etc, 261

Steinkuller, P: *see* Whitfield, R, etc, 333

Stempels, N: *see* Salu, P, etc, 53

Stevens, J D (*Correspondence*): Viscoelastic agents in ocular surgery, 512

Stone, R D: *see* Char, D H, etc, 183

Strachan, I: *see* West, J, etc, 511

Strachan, I M: *see* Leitch, R J, etc, 278

Streeten, B W: *see* Dark, A J, etc, 717

Stroh, E M, Finger, P T: Traumatic transconjunctival orbital emphysema, 380

Sunder Raj, P, Akingbehin, T, Levy, A M: Objective autorefraction in posterior chamber pseudophakia, 731
Suttorp-Schulten, M S A, Koornneef, L: Linear scleroderma associated with ptosis and motility disorders, 694
Swartwood, J: *see* Whitfield, R, etc, 333
Swenson, M R: *see* Katz, B, etc, 706

Tabbara, K F, Al-Kassimi, H: Ocular brucellosis, 249
——: *see* Al-Haddab, S, etc, 123
Takigawa, Y: *see* Fujiwara, H, etc, 631
Talbot, J: *see* Benson, M T, etc, 251
Tarlton, J F, Easty, D L: Immunohistological characterisation of retinoblastoma and related ocular tissue, 144
Taylor, D: *see* Amaya, L G, etc, 150
——: *see* Hing, S, etc, 73
Taylor, D S I: *see* Russell-Eggitt, I, etc, 136, 421
Taylor, H R: *see* West, S K, etc, 12
Taylor, J L: *see* O'Brien, W J, etc, 723
Teoh, Su Lin, Allan, D, Dutton, G N, Foulds, W S: Brightness discrimination and contrast sensitivity in chronic glaucoma – a clinical study, 215
Tessler, H H, Jennings, T: High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's disease, 353
Tessler, Z: *see* David, R, etc, 272
Thaker, U: *see* Babalola, O E, etc, 89
Thiru, A A A: *see* O'Connor, G M, etc, 245
Thompson, J R: *see* Wang Yu-dong, etc, 650
Thompson, R A: *see* Hansel, T T, etc, 118
Thulador, L: *see* Brandt, F, etc, 14
Ticho, U: *see* Backon, J, etc, 607
Timonen, P: *see* BenEzra, D, etc, 350
Treister, G: *see* Cahane, M, etc, 382
Trope, G E: *see* Finkelstein, I, etc, 280
——: *see* Smith, D A, etc, 605
Tuft, S J, Fitzke, F W, Lawrenson, J, Silver, J, Marshall, J: Quantification of lens opacification with a commercially available lensometer, 78
Tyers, A G: *see* Ragge, N K, etc, 561

Ueno, S: *see* Fujiwara, H, etc, 631
Ukai, K: *see* Mezawa, M, etc, 472

Vaghela, B: *see* Shine, B S F, etc, 427
Vanden Houte, K: *see* Salu, P, etc, 53
Vannas-Sulonen, K: *see* Raitta, C, etc, 363
Verbeelen, D: *see* Salu, P, etc, 53
Verbraak, F D: *see* van den Berg, W, etc, 696
Vernon, S A, Henry, D J, Jones, S J: Calculating the predictive power of the Henson field screener in a population at risk of glaucomatous field loss, 220
——: *see* Clarke, M P, etc, 526
——: *see* West, J, etc, 243
Vighetto, A: *see* Grochowicki, M, etc, 358
Vogel, R, Crick, R P, Newson, R B, Shipley, M, Blackmore, H, Bulpitt, C J: Association between intraocular pressure and loss of visual field in chronic simple glaucoma, 3
de Vries, J, Baarsma, G S, Zaal, M J W, Boen-Tan, T N, Rothova, A, Buitenhuis, H J, Schweitzer, C M C, de Keizer, R J W, Kijlstra, A: Cyclosporin in the treatment of severe chronic idiopathic uveitis, 344

Walker, C: *see* Ingram, R M, etc, 82
Walsh, G P: *see* Hussein, N, etc, 647
Walters, R F, Spalton, D J: Central retinal vein occlusion in people aged 40 years or less: a review of 17 patients, 30
Wang Yu-dong, Thompson, J R, Goulstine, D B, Rosenthal, A R: A survey of the initial referral of children to an ophthalmology department, 650
Ward, D L: *see* Spaide, R F, etc, 465
Wasserman, D: *see* Geyer, O, etc, 242
Watanabe, R: *see* Ishibashi, Y, etc, 433
Watson, A P, Rosen, E S: Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules, 458
Watts, J (*Correspondence*): Corneal amyloidosis, 320
Weinreb, R N: *see* Katz, B, etc, 99
Weisman, G D: *see* Finger, P T, etc, 121
Weiss, A: *see* Hirsh, A, etc, 638
Weissman, S S, Asbell, P A: Effects of topical timolol (0·5%) and betaxolol (0·5%) on corneal sensitivity, 409
Welsh, N H: *see* Carmichael, T R: *see* 528
West, J, Longstaff, S: Topical timolol and serum lipoproteins, 663
West, J, Burke, J P, Strachan, I (*Correspondence*): Carbamazepine, epilepsy, and optic nerve hypoplasia, 511
——, **Askin, G, Clarke, M, Vernon, S A:** Loss of vision in one eye following scoliosis surgery, 243
West, S K, Taylor, H R: Reliability of photographs for grading trachoma in field studies, 12
Wheatcroft, S M: *see* Hykin, P G, etc, 499
Wheeler, D T: *see* Katz, B, etc, 99
Whitacre, M M, Manoukian, N, Mainster, M A: Argon indirect ophthalmoscopic photocoagulation: reduced potential phototoxicity with a fixed safety filter, 233
White, V A: *see* Antle, C M, etc, 502
Widerholt, M: *see* Wiek, J, etc, 665
Wiek, J, Schade, M, Wiederholt, M, Arntz, H R, Hansen, L L: Haemorheological changes in patients with retinal vein occlusion after isovolaemic haemodilution, 665
Wiersinga, W M: *see* Mourits, M Ph, etc, 481
Williams, A: *see* Winfield, A J, etc, 477
Williams, A C: *see* Corridan, P, etc, 309
Williams, D F, Mieler, W F, Jaffe, G J, Robertson, D M, Hendrix, L: Magnetic resonance imaging of juxtapapillary plaques in cadaver eyes, 43
Winfield, A J, Jessiman, D, Williams, A, Esakowitz, L: A study of the causes of non-compliance by patients prescribed eyedrops, 477
Wojnarowska, F: *see* Frith, P, etc, 163
Wolf, R: *see* Hussein, N, etc, 647
Wong, D, Kaye, S B (*Correspondence*): Chart for visual acuity screening, 125
Wood, C M, Richardson, J: Chorioretinal neovascular membranes complicating contusional eye injuries with indirect choroidal ruptures, 93
————: Indirect choroidal ruptures: aetiological factors, patterns of ocular damage, and final visual outcome, 208
——: *see* Chowdhury, C R, etc, 445
Woon, W H, Spalton, D J: A computerised diagnostic index for medical and neuro-ophthalmology, 212
Wormser, G P: *see* Kauffmann, D J H, etc, 325
Wortham, C: *see* Stayte, M, etc, 465
Wright, J E: *see* Hakin, K N, etc, 496
——: *see* Hunter, J V, etc, 505
Wyse, R K H: *see* Russell-Eggitt, I M, etc, 421

Yagev, R: *see* David, R, etc, 272
Yamamoto, Y: *see* Furuse, N, etc, 258
Yannuzzi A: *see* Spaide, R F, etc, 536
Yarian, D L: *see* Leff, S R, etc, 498
Yassur, Y: *see* David, R, etc, 272
Yee, M L: *see* Hansel, T T, etc, 118
Yokayama, C: *see* Hakin, K N, etc, 496
——: *see* Hunter, J V, etc, 505
Yung Yen, M, Hon Liu, J, Ji Jaw, S: Ptosis as the early manifestation of pituitary tumour, 188

Zaal, M J W: *see* de Vries, J, etc, 344
Zalta, A H, Burchfield, J C: Detecting early glaucomatous field defects with the size I stimulus and Statpac, 289
Zaltas, M: *see* Hemady, R, etc, 26
Zang, E: *see* Abramson, D H, etc, 359
Zeki, S M: Optic nerve hypoplasia and astigmatism: a new association, 297
——, **Dutton, G N:** Optic nerve hypoplasia in children, 300
Zhou, H M: *see* Brandt, F, etc, 14
Zuccheto, M: *see* Midena, E, etc, 106

VOLUME 41 · SUBJECT INDEX

***Acanthamoeba*:**
  contamination, contact lens storage cases, 129, 133
  keratitis, experimental, 551
Accommodation, pseudophakic, 22
Acetazolamide, tablets and sustets, effects compared, in chronic simple glaucoma, 413
Acuity, visual:
  final, after indirect choroidal rupture, 208
  lens opacity meter reading and, age and, correlations, 78
  screening, chart for, 125
Acyclovir:
  in chickenpox chorioretinitis, 698
  local and systemic compared, in hepatic disciform keratitis, 283
  reduced sensitivity to, in ocular herpes simplex virus infections, 286
Adenocarcinoma, mucinous, metastatic to iris, ciliary body and choroid, 373
Adenoma, pituitary, contrast sensitivity and, 358
Adenovirus keratitis, *see* Keratitis
Age/Aging:
  lens, precapsular film on, psendoexfoliation precursor? 717
  40 or under, central retinal vein occlusion and, 30
AIDS:
  adult gonococcal keratoconjunctivitis and, 52
  choroidal lesions in, 610
  intravitreal ganciclovir for cytomegalovirus retinitis in, 511
  retinal dysfunction as initial ophthalmic sign in, 49
Albinism, in children, flash VEP and ERG study, 136
Aldosteronism, pre-eclampsia and, choriocapillaris, lobular pattern, in, 702
Amblyopia:
  detection, children, 650
  patching, stopping, safe time for, 709
  relative afferent pupillary defects (RAPD) in, 676
  severe, prevention, 158
  strabismic, diagnosis, family history of strabismus and, 589
  tobacco, yellow forelock and, 509
Amitosis, in donor corneal endothelium, 63
Amyloidosis, corneal, 320
Anaesthesia:
  local, cataract extraction and: 639
    extracapsular, 195, 203, 205
    without retrobulbar injection, 639
  non-retrobulbar, extracapsular extraction and, 195, 203, 205
  subconjunctival injection, extracapsular extraction and, 195, 203, 205
Angiography, fluorescein:
  optic nerve avulsion, traumatic, and, 500
  oral, relative safety, reassessment, capsules and, 458
  video, computer assisted analysis, 275
Angioid streaks, incidence in Pagets' disease of bone, 577, 579
Aniridia, 11p 13 deletion and Wilms' tumour and, 568
Anterior chamber, shallow, angle closure glaucoma, axial hypermetropia and Fuchs's dystrophy and, 601
Anterior segment, surgery, review, 368
Antigen, HLA-DR2, specificity, lack, multifocal choroiditis and panuveitis and, 536
Aphakia:
  epikeratophakia for, 67
  infant, contact lenses for, 150
Assault, with chemicals, ocular injuries and, 513, 514
Astigmatism:
  optic nerve hypoplasia and, 297
  surgery for, 368
Award, David Cole travel fellowship, 256

***Bacillus*,** endophthalmitis, case series and review, 26
Bacteria, contact lens storage case contamination by, 129
Behçet's disease, chlorambucil in, 353
Betaxolol, corneal sensitivity and, 409
Biofeedback treatment, waveform changes in congenital nystagmus and, 472
Biometry, lens, in early-onset diabetes, 654
Biomicroscopy, fundus, +150 dioptre lens and, 294
Biostatistics, evidence for two chronic open-angle glaucoma populations and, 196
Blepharospasm, botulinum toxin injection in, acute-angle closure glaucoma following, 309
Blind/Blindness:
  cataract and, epidemiology and projections, India, 341
  eye disease and, Kenya, 333
  prevalence, Turkana tribe, Kenya, 85
Blink, frequency, rigid contact lens wear and, corneal oxygenation and, 168
Blood:
  deoxygenated, viscosity, in diabetic retinopathy, 400
  red cell aplasia, adult pure, topical ocular chloramphenicol and, 640
  whole, viscosity, changes, isovolaemic haemodilution for retinal vein occlusion and, 665
Blood-aqueous barrier, ocular fluorophotophotometry and, 431
Blood-retinal barrier:
  leakage, local, retinal light sensitivity in diabetic retinopathy and, 388
  ocular fluorophotophotometry and, 431
Body, position, altered, β-blocker effect on, 605
Bone, frontal, epidermoid, proptosis due to, 445
Book Reviews:
  Benson, W E, Brown, G C, Tasman, W: Diabetes and its Ocular Complications, 1988, 225
  Bodis-Waller, I, Piccolino, M (Eds)· Neurology and Neurobiology, Vol 43 Dopaminergic Mechanisms in Vision, 1988, 126
  Carpenter, R H S: Movements of the Eyes, 2nd Edn, 1988, 320
  Char, D H Clinical Ocular Oncology, 1989, 125
  Chignell, A H: Retinal Detachment Surgery, 2nd Edn, 1988, 127
  Cline, D, Hofstetter, H W, Griffin J R. Dictionary of Visual Science, 4th Edn, 1989, 511
  Deutsch, T A· Ophthalmic Clinical Debates, 1989, 192
  von Euler, C, Lundberg, I, Lennerstrand, G (Eds): Brain and Reading, 1989, 255
  Freeman, H MacK, Tolentino, F I (Eds): Proliferative Vitreoretinopathy (PVR), 1988, 255
  Friedlaender, M H (Ed): Prevention of Eye Disease, 1988, 192
  Galloway, N R, Verson, S A: Ophthalmology, 127
  Gardner, M J, Altman, D G: Statistics with Confidence: Confidence Intervals and Statistical Guidelines, 1989, 128
  Hersh, P S: Ophthalmic Surgical Procedures, 1989, 128
  International Agency for the Prevention of Blindness (Ed): World Blindness and its Prevention, Vol 3, 1988, 127
  Kanski, J J: Clinical Ophthalmology, 2nd Edn, 1989, 255
  Kennard, C, Clifford Rose, F (Eds): Physiological Aspects of Clinical Neuro-Ophthalmology, 1988, 128
  Kohn, R.: Textbook of Ophthalmic Plastic and Reconstructive Surgery, 1988, 447
  Krupin, T: Manual of Glaucoma· Diagnosis and Management, 1988, 126
  Lennerstrand, G, von Noorden, G K, Campos, E C (Eds): Wenner-Gren International Symposium Series. Vol 49, Strabismus and Amblyopia, 1988, 320
  Levine, M R (Ed): Manual of Oculoplastic Surgery, 448
  Miller, N R: Walsh and Hoyt's Clinical Neuro-Ophthalmology, 4th Edn, Vol 3, 1988, 127
  Piatigorsky, J, Shinohara, T, Zelenka, P S (Eds): Molecular Biology of the Eye: Genes, Vision, and Ocular Disease, 126
  Regan, D: Human Brain Electrophysiology· Evoked Potentials and Evoked Magnetic Fields in Science and Medicine, 1989, 255
  Rootman, J: Diseases of the Orbit, 1988, 126
  Ruben, M: A Colour Atlas of Contact Lenses and Prosthetics, 2nd Edn, 1989, 255
  Simmons Lessell and van Dalen, J T W (Eds): Current Neuro-Ophthalmology, 1988, 125
  WHO/UNICEF/IVACG Task Force: Vitamin A Supplements, 1988, 64
  Wilson, M S, Millis, A E W. Contact Lenses in Ophthalmology, 1989, 192
  Yanoff, M, Fine, B S: Ocular Pathology: A Colour Atlas, 1988, 128
Botulinum toxin, injection in blepharospasm, acute-angle closure glaucoma following, 309
Brightness, discrimination, in chronic glaucoma, 215
***British Journal of Ophthalmology*:**
  fifty years ago, 704
  in the 1990s, 1
British Orthoptic Society, 640
Brucellosis, ocular, uveitis and, 249
Bruton's disease, infective conjunctivitis and corneal scarring in, in sibs, 118

***Candida albicans*:**
  keratitis, fluconazole for (rabbit), 40
  mixed haematogenous endophthalmitis and, 247
Carbamazepine, epilepsy and optic nerve hypoplasia and, 511
Cataract:
  aqueous and serum zinc and copper concentrations in, 661
  blindness due to, Kenya, 333
  congenital, extraction, 66
  extraction: anaesthesia, local, for, 639
    children, 73
    extracapsular: persistently raised intraocular pressure after, 272

Cataract – *continued*
      stabilisation of refraction after, wound closure technique and, 486
      without retrobulbar anaesthetic injection, 195, 203, 205
    indomethacin, topical, on day and, 19
    results and complications, Saudi Arabia, 141
    review, 368
    streptokinase administration after, total hyphaema and, 447
    subconjunctival gentamicin and cefuroxime, toxicity compared in, 734
  fluorosilicone oil in retinal detachment surgery and, 643
  prevalence in Paget's disease of bone, 579
  senile, Turkana tribe, Kenya, 84
  surgeons, shortage, 324
CDC corynebacterium, group A-4, mixed haematogenous endophthalmitis and, 247
Cefuroxime, subconjunctival, gentamicin and, toxicity compared, 734
Cell biology, advances, 186
CHARGE association, eye in, 421
Chemicals, assault with, ocular injury and, 513, 514
Chickenpox:
  adult, retinal necrosis in, 443
  chorioretinitis, acyclovir in, 698
Child/Children:
  albinism in, flash VEP and ERG study, 136
  contact lenses for aphakia in, 150
  esotropia, secondary, surgery for, binocularity and, 155
  high-risk, strabismus and neurological disorders, incidence, in, 465
  hypermetropia, abnormal, treatment from age of 6 months, 158
  infectious mononucleosis presenting as acute dacryocystitis in, 750
  initial referral to ophthalmology department, survey, 650
  lens surgery in, case series analysis, 73
  optic nerve hypoplasia, review, 300
  poor vision, initial detection in, 650
  stopping patching in, 709
  trial frame for, 639
  visual acuity factors in, convergent strabismus treatment and, 82
Chlorambucil, high-dose short-term, in intractable sympathetic ophthalmia and Behçet's disease, 353
Chloramphenicol, topical, ocular, adult pure red cell aplasia following, 640
Choriocapillaris, lobular pattern in pre-eclampsia with aldosteronism, 702
Chorioretinal:
  gyrate atrophy, ERG of neural retina and pigment epithelium in, 363
  neovascular membranes, contusion injuries with indirect choroidal ruptures and, 93
Chorioretinitis, chickenpox, acyclovir in, 698
Choristoma, osseous, atypical, 700
Choroid/Choroidal:
  haemorrhage, disseminated, miliary tuberculosis and, 317
  lesions, AIDS and, 610
  melanoma: malignant, extrascleral spread, postenucleation orbital radiotherapy for, 36
    radioimmunoscintigraphy with monoclonal antibodies to melanoma associated antigens and, 538
  mucinous adenocarcinoma metastatic to, 373
  neovascularization, iatrogenic, outcome in sickle cell disease, 417
  osteoma, atypical, 700
  rupture, indirect: case series analysis, 208
    contusional eye injuries and, chorioretinal neovascular membranes complicating, 93
Choroiditis, multifocal, lack of HLA-DR2 specificity in, 536
Chromosome, 11p 13 deletion, Wilms' tumour and aniridia and, 568
Cilia, ectopic, originating from iris, atraumatic, 748
Ciliary, body:
  melanoma, optic nerve invasion and, 123
  mucinous adenocarcinoma metastatic to, 373
Collagen:
  classification, 386
  content, in trabecular meshwork, glaucoma and, 280
  types I-IV, distribution in aging retinal vessels, 228
Coloboma, ocular, CHARGE association and, 421
Colour vision:
  loss, in anterior ischaemic optic neuropathy, 99
  molecular genetics and, 238
Computer, fluorescein videoangiogram analysis and, 275
Computerised diagnostic index, for medical and neuro-ophthalmology, 212
Congenital, lid retraction, management, 542
Congresses:
  AIDS and vision loss, San Francisco, January, 1990, 64
  Asian and Oceanian Physiological Societies, satellite symposium, Cochin, November 1990, 640
  British Ophthalmic Photographic Association, VI Annual Conference, Edinburgh, November 1990, 640
  Diabetic Retinopathy workshop, London, October 1990, 256
  German Ophthalmological Society, International Symposium on ocular infections, Bonn-Köln, September 1991, 640
  Hong Kong Ophthalmological Society meeting, December 1990, 640
  International Agency for the Prevention of Blindness, IVth General Assembly, Nairobi, November 1990, 256
  International Perimetric Society, IXth Meeting, Malmo, June 1990, 192
  International Symposium on Ocular Inflammation, Alicante, May 1990, 256
  IInd International Symposium on Ocular Trauma, Geneva, April 1992, 448
  XXX Nordic Ophthalmological Meeting, Helsinki, August 1991, 384
  Ocular Pharmacology and Therapeutics Symposium, New Delhi, August 1990, 125
  IVth Paediatric Surgery Workshop, Berlin, June 1991, 640
  Panhellenic Ophthalmological Society, Congresses 1990, 125
  Welsh Cataract Congress, Houston, Texas, September 1990, 125
Conjunctiva/Conjunctival:
  biopsy, sarcoidosis, diagnosis, and, 469
  histiocytoma, fibrous, malignant, 624
  limbal, inferior, trauma, hard contact lenses and, 519
  lymphangioma circumscriptum, 574
  melanoma, malignant, therapeutic outcome, case series, 615
  pigment dispersal through, after repaired traumatic perforation, 257
  rhinosporidiosis, scleral melting in, 635
  scarring, lupus erythematosus and, 163
  staining, conjunctival tear film and, 519
  tear film, staining and, 519
  tuberculosis, neighbouring lupus vulgaris lesion and, 315
Conjunctivitis:
  haemorrhagic, acute, outbreak, Kaduna, Nigeria, 89
  infective, corneal scarring and, in sibs with Bruton's disease, 118
  purulent, prevalence, Turkana tribe, Kenya, 85
Contact lenses:
  hard, traumatising inferior limbal conjunctiva, 519
  infant aphakia and, 150
  ophthalmoscopic, for retinal photocoagulation, magnification, spot size and field of view, 177
  rigid-wear, blink frequency in, corneal oxygenation and, 168
  storage cases, contamination, 129, 133
Contrast sensitivity:
  in chronic glaucoma, 215
  peripheral, in glaucoma and ocular hypertension, 712
  in pituitary adenoma, 358
Copper, aqueous and serum concentrations, in glaucoma and cataract, 661
Cornea/Corneal:
  amyloidosis, 320
  diameter, measurement, 63, 64
  donor:
    adult and infant, endothelium, damage, manipulative, 261
    endothelium, amitosis in, 63
    parameters: acuity recovery after keratoplasty and, 7
      primary graft failure and, 7
    storage media compared, 7
  endothelium, dystrophy, Fuchs', axial hypermetropia, shallow anterior chamber and angle closure glaucoma and, 601
  epithelium, erosion, total, bilateral, cytotoxic therapy and, 638
  oedema, herpetic eye disease and pathogenesis (rabbit), 723
  oxygenation, blink frequency and rigid contact lens wear and, 168
  pannus, Wilms' tumour and aniridia and, 568
  replica technique, adenovirus keratitis, cytopathology, and, 670
  scarring, in Bruton's disease, in sibs, 118
  sensitivity, timolol and betaxolol and, 409
  stroma, disease, herpes simplex (rabbit), 723
  surgery, review, 368
  tissue, supply in United Kingdom, 685
  Transplant Service, 685
  ulcer, treatment, topical steroids, 528
Courses:
  Intraocular Trauma Course, Antwerp, October 1990, 256
  Paediatric Ophthalmology Course, Tunis, September 1990, 125
  Standardised echography in ophthalmology, Munich, October 1990, 576
Cowpox, ocular, transmission from cat to man, 245
Cryotherapy:
  conjunctival malignant melanoma and, 615
  retinopathy in incontinentia pigmenti and, 377
Cyclocryotherapy, case series review, 103
Cyclosporin:
  A, ocular penetration, in man, 350
  in severe chronic uveitis, 344
Cyst, aneurysmal bone, sphenoid, orbit and, 505
Cysticercus cellulosae, infestation of extraocular muscle, 751
Cystinosis, nephrotic, photic sneeze reflex in, 705, 706
Cytology, impression, optimum surface for, 254
Dacryocystitis, acute, bilateral, infectious mononucleosis presenting as, 750
Dapsone, leprosy and, iris histopathology and, 14
Diabetes:
  accelerated ocular neovascularisation in, posterior chamber lens implant and, 313
  corneal endothelial changes after posterior chamber lens implantation and, 257, 258

Diabetes – *continued*
  early-onset, crystalline lens biometry in, 654
  macular recovery function testing in, value, 106
  retinal function and, 385, 704
  scotomata in, 704
Disease:
  ocular, blindness and, Kenya, 333
  ophthalmic, prevalence, Turkana tribe, Kenya, 84
  sickle cell, haemoglobin, retinopathy and, 172
    homozygous retinopathy and, 172
    iatrogenic choroidal neovascularisation, outcome, in, 417
  thromboembolic, longstanding, central retinal artery occlusion and, homocystinuria presenting as, 696
Drug abuse, self-enucleation and, 571
Dysplasia, septo-optic, astigmatism and, 297

Echography, β-scan, choroidal osteoma and, 700
Ectopia lentis, lensectomy for, 66, 73
Electrophoresis, aqueous and serum neurone-specific enolase, assessment, in retinoblastoma and ocular melanoma, 427
Electroretinogram/Electroretinography:
  albinism in children and, 136
  diffuse flash, in minimal diabetic retinopathy, 681
  neural retina, in chorioretinal gyrate atrophy, 363
  pattern: in amblyopia, 676
    in minimal diabetic retinopathy, 681
  pigment epithelium, in chorioretinal gyrate atrophy, 363
Endophthalmitis:
  Bacillus-induced, case series and review, 26
  Lyme disease and, 325
  mixed haematogenous, 247
  Nocardia asteroides, systemic lupus erythematosus and, 433
Enolase, neurone-specific, aqueous and serum, assessment, retinoblastoma and ocular melanoma and, 427
Enophthalmos, hemifacial atrophy causing, 496
Enucleation, self-, psychosis and, 571
Epikeratophakia:
  for aphakia, keratoconus, and myopia, 67
  with biological adhesive, 384
Epilepsy, carbamezipine for, optic nerve hypoplasia and, 511
Epiretinal membranes:
  components, variation, time and, 393
  natural history, 386
Episcleritis, lupus erythematosus and, 163
Esotropia, convergence excess, treatment, operative, 278
Exfoliation syndrome:
  immunogold localisation of laminin in iris in, 450
  material, source, 449
Exophthalmos, frontal bone epidermoid causing, 445
Eye/Eyes:
  CHARGE association and, 421
  defects, in geographically defined population of 2-year-olds, 465
Eye Bank, Corneal Transplant Service, 685
Eyedrops, prescription, patient non-compliance, causes, and, 477

Fibrinogen, adhesive, epikeratophakia and, 384
Fields, visual:
  charts, compact, 704
  defects: diabetes and, 704
    glaucomatous, early detection, size/stimulus and Statpac and, 289
    optic nerve avulsion due to rotation of globe by snooker cue and, 499
  deficits, computerised, in retinal pigment epithelial tears, 556
  Henson screener, predictive value in glaucoma, 220
  kinetic, in tobacco amblyopia, 509
  loss, association with intraocular pressure, in chronic simple glaucoma, 1, 3
  ptosis in pituitary tumour and, 189
Fluconazole, in *Candida albicans* keratitis (rabbit), 40
Fluorescein angiography, *see* Angiography
Fluorosilicone oil, in retinal detachment surgery, 641, 643
5-Fluorouracil, corneal epithelial erosion following, 638
Fluorophotophotometry, ocular, review, 431
Foreign bodies, intra-ocular, non-magnetic, removal, lithotrite and, 576
Fundus, biomicroscopy, +150 dioptre lens and, 294
Fusion, convergence excess esotropia, treatment, and, 278

Ganciclovir, intravitreal, for cytomegalovirus retinitis in AIDS, 511
Gentamicin, subconjunctival, cefuroxime and, toxicity compared, 734
Glaucoma:
  angle-closure: acute:
      botulinium toxin injection for blepharospasm and, 309
      iridotomy size in, 583
      Nd-YAG laser iridotomy and, 523
    shallow anterior chamber, axial hypermetropia, and Fuchs's dystrophy and, 601
  aqueous and serum zinc and copper concentrations in, 661
  blindness due to, Kenya, 333
  chronic:
    brightness discrimination and contrast sensitivity in, 215
    simple. acetazolamide tablets and sustets compared in, 413
      intraocular pressure and field loss, association, in, 1, 3
      subgroups, 2
  developmental, treatment, laser goniotomy, 384
  field defects, early detection, in, size/stimulus and Statpac and, 289
  Henson field screener, predictive power in, 220
  intraocular pressure decrease in, induced functional vagotomy and, 607
  levobunolol and, 605
  malignant, after laser iridotomy, pilocarpine and central retinal vein thrombosis and, 576
  open-angle:
    chronic, biostatistical evidence for two distinct populations, 196
    primary, diode laser trabeculoplasty for, 743
  peripheral contrast sensitivity in, 712
  secondary, iris melanoma and, 566
  siblings with Morquio syndrome and, 382
  trabecular meshwork collagen content and, 280
  treatment, operative, cyclocryotherapy, case series review, 103
  uveitis and, retrospective study, 223
Globe, perforation, inadvertent, incidence in strabismus surgery, 490
Goniotomy, laser, in developmental glaucoma, 384
Gonorrhoea, keratoconjunctivitis due to AIDS and, 52

Haematocrit, changes, isovolaemic haemodilution for retinal vein occlusion and, 665
Haemodilution, isovolaemic, for retinal vein occlusion, haemorheological change after, 665
Haemophilia, traumatic hyphaema and, 565
Haemorheology, changes, after isovolaemic haemodilution for retinal vein occlusion, 665
Hansen's disease, intraocular pressure and (monkey), 647
Hemianopia, bitemporal, pituitary tumour and, 189
Hemifacial atrophy, enophthalmos due to, 496
HELLP syndrome, vitreous haemorrhage in, 498
Histoplasmosis, syndrome, presumed ocular, HLA-DR2 and, 536
Homocystinuria, central retinal artery occlusion and longstanding thromboembolic disease and, 696
Hydroxypropylmethyl cellulose, ocular surgery and, 512
Hypermetropia:
  abnormal, treatment from age of 6 months, 158
  meridional, abnormal, convergent strabismus, treatment, outcome, and, 82
Hypertension,
  ocular: diode laser trabeculoplasty for, 743
    peripheral contrast sensitivity in, 712
  risk factor for retinal macroaneurysms, 595
Hyphaema:
  total, following streptokinase, after cataract extraction, 447
  traumatic, in haemophiliac, 565
Hypogammaglobulinaemia, sex-linked, infective conjunctivitis and corneal scarring and, in sibs, 118

Immunoglobulins, in vitreous and subretinal fluids, in rhegmatogenous retinal detachment, 160
Immunogold labelling, collagen types I-IV, distribution in aging retinal vessels, and, 228
Immunohistochemistry, advances, 186
Immunohistology, characterisation of retinoblastoma and related ocular tissue, 144
Immunoscintigraphy, *see* Radioimmunoscintigraphy
Inclusion bodies, in adenovirus keratitis, 670
Incontinentia pigmenti, retinopathy in, early diagnosis and treatment, 377
India, cataract blindness in, projections, 341
Indomethacin, topical, day of cataract extraction, 19
Injury, ocular:
  Bacillus endophthalmitis following, prevention, 26
  chemicals, assault with, causing, 513, 514
  contusional, chorioretinal neovascular membranes complicating, indirect choroidal ruptures and, 93
  indirect choroidal rupture and, case series analysis, 208
  optic nerve avulsion due to, 499
  perforating, external ocular pigmentation secondary to, 251
Intraocular lens, *see* Lens implant
Intraocular pressure:
  altered body position and, β-blocker effect and, 605
  changes, postural, in Hansen's disease (monkey), 647
  cyclocryotherapy and, 103
  decrease in glaucoma, induced functional vagotomy and, 607
  diurnal, acetazolamide tablets and sustets, effects on compared, in chronic simple glaucoma, 413
  field loss, association with, in chronic simple glaucomna, 1, 3
  MK-927, single dose, and, 405
  optic neuropathy, anterior ischaemic, and, 99
  persistently raised, after extracapsular cataract extraction, 272

Iridotomy:
  laser: malignant glaucoma following, pilocarpine and central retinal vein thrombosis and, 576
    Nd-YAG, in acute angle-closure glaucoma, 523
  size, in acute-angle closure glaucoma, 583
Iris:
  absorption of scattered light, pupil size affecting measurements made with Lens Opacity Meter 701 and, 526
  biopsy, electron microscopy, in Refsum's disease, 370
  cilia, atraumatic, and, 748
  histopathology, in dapsone-treated leprosy patients, 14
  laminin localisation in, immunogold label and, 450
  melanoma, progression over 41 years, 566
  mucinous adenocarcinoma metastatic to, 373
Iritis, in acute haemorrhagic conjunctivitis, 89

Kaduna, Nigeria, acute haemorrhagic conjunctivitis outbreak in, 89
Kenya:
  ophthalmic disease, prevalence in Turkana tribe in, 84
  Rural Blindness Prevention Project, survey results, 333
Keratitis:
  Acanthamoeba, experimental, 551
  adenovirus, cytopathology, replica technique and, 670
  Candida albicans, fluconazole for (rabbit), 40
  in contact lens users, causes, 129
  disciform, herpetic, acyclovir, local and systemic compared in, 283
  fungal, *Scopulariopsis brevicaulis* causing, 561
Keratoconjunctivitis, gonococcal, adult, AIDS and, 52
Keratoconus, epikeratophakia for, 67
Keratometer, Canon RK-1 Autoref, in pseudophakia, 731
Keratoplasty:
  acuity recovery after, donor parameters and, 7
  conjunctival malignant melanoma and, 615
  graft failure, donor parameters and, 7
Kidney, transplantation, lens after, 267

Labour, orbital haemorrhage due to, 242
Lagophthalmos, management, patient ingenuity in, 254
Laser:
  diode, trabeculoplasty, 743
  iridotomy, malignant glaucoma following, pilocarpine and central retinal vein thrombosis and, 576
  Nd-YAG, iridotomy, acute angle-closure glaucoma and, 523
Lens (crystalline):
  after renal transplantation, 267
  aging, precapsular film on, pseudoexfoliation precursor?, 717
  autofluorescence study, 431
  biometry, in early-onset diabetes, 654
  capsule, anterior, subtle opacification, age and, 717
  cataractous, sterol content, in cerebrotendinous xanthomatosis II, 629
  histology in Weill-Marchesani syndrome, 631
  opacification, quantification by lensometer, 78
  Opacity Meter 701 measurements, pupil size and, 526
  parameters, changes, early-onset diabetes and, 654
  surgery, in infants and children, case series analysis, 73
Lens implant:
  posterior chamber: accelerated ocular neovascularisation after, in diabetics, 313
    implantation, corneal endothelial change after, diabetes and, 257, 258
      objective autorefraction and, 731
  psueodophakic accommodation and, 22
  safety, 257
Lensometer, lens opacification quantification with, 78
Leprosy, dapsone-treated. iris histopathology in, 14
Levobunolol, effect on altered body position, intra-ocular pressure and, 605
Lid/Lids:
  lower, margin, erosion, lupus erythematosus and, 163
  lymphangioma circumscriptum, 574
  retraction, congenital, management, 542
  upper:
    retraction, aetiology in Graves' ophthalmopathy, 484
    trichiasis, surgery, standardised, in, trachoma and, 109
Lipoproteins, serum levels, topical timolol and, 663
Liposarcoma, orbital, CAT findings in, 437
Lithotrite, foreign body removal and, 576
Lupus:
  erythematosus:
    cutaneous, chronic, external ocular findings in, 163
    systemic: external ocular findings in, 163
      Nocardia asteroides endophthalmitis and, 433
  vulgaris, facial, conjunctival tuberculosis and, 315
Lye, ocular injury and, 513
Lyme disease, ocular, 325
Lymphangioma, circumscriptum, lid and conjunctiva, 574

Macula/Macular:
  degeneration, incidence in Paget's disease of bone, 569
  hole, retinal detachment, treatment, 201
  recovery function in diabetics, 106
Magnetic resonance imaging: 494
  juxtapapillary plaques, cadaver eyes, 43
Melanoma:
  choroidal, radioimmunoscintigraphy with monoclonal antibodies to melanoma associated antigens and, 538
  ciliary body, optic nerve invasion and, 123
  intraocular, management, review, 559
  iris, progressing over 41 years, 566
  juxtapapillary, magnetic resonance imaging and, 43
  malignant:
    conjunctival, therapeutic outcome, case series, 615
    intraocular, with extrascleral extension, postenucleation orbital radiotherapy and, 36
    ocular, aqueous and serum neurone-specific enolase assessment in, 427
      radioimmunoscintigraphy in, 254
Microphthalmos:

  in CHARGE association, 421
  colobomatous orbital cyst and, 59
Microscopy, electron:
  collagen types I-IV, distribution in aging retinal vessels, 228
  conjunctiva, external pigmentation secondary to perforating eye injury and, 251
  iris biopsy, in Refsum's disease, 370
  lens, in Weill-Marchesani syndrome, 631
  scanning:
    corneal endothelium, donor, amitosis and, 63
    donor corneae, manipulation, endothelial damage, and, 261
    microphthalmos and orbital cyst, 59
    precapsular film on aging lens, pseudoexfoliation and, 717
  transmission, microphthalmos and orbital cyst, 59
  uveitis, multifocal posterior, 688
Miosis, surgically induced, prevention, indomethacin, 19
MK-927, single dose, intraocular pressure reduction and, 405
Molecular biology, advances, 186
Monoclonal antibodies, to melanoma associated antigens, radioimmunoscintigraphy and, in choroidal melanoma, 538
Mononucleosis, infectious, presenting as acute dacryocystitis, 750
Morning glory syndrome, histopathological study, 56
Morquio syndrome, glaucoma and, in sibs, 382
Movements, ocular:
  adduction, failure, after orbital decompression, 239
  disorders:
    ptosis and linear scleroderma and, 694
    vertical, in CHARGE association, 421
Mucopolysaccharides, in chamber angle, glaucoma in Morquio syndrome and, 382
Muscles, extraocular:
  Cysticercus cellulosae infestation, 751
  surgery, in Graves' ophthalmopathy, 481
Myopia:
  aetiology, 47
  deprivation (animals), 47
  epikeratophakia for, 67

Nephritis, tubulointerstitial, acute, uveitis and, syndrome, in elderly woman, 53
Neurofibromatosis, von Recklinghausen's, uveal melanoma and optic nerve glioma in, 502
Neuro-ophthalmology:
  computerised diagnostic index for, 212
  review, 494
Neuroradiology, 494
Nigeria, acute haemorrhagic conjunctivitis outbreak in, 89
***Nocardia asteroides*:**
  endophthalmitis, systemic lupus erythematosus and, 433
Nyctometry, value in diabetes screening and follow-up, 106
Nystagmus:
  in CHARGE association, 421
  congenital, waveform changes, biofeedback treatment and, 472
  incidence in population of 2-year-olds, 465

Octopus, computerised visual fields analysis, retinal pigment epithelial tears and, 556
***Ophthalmic Review*,** 1
Ophthalmic surgerys:
  artificial maintenance of relative ocular tissue pressure during, 462
  intraocular, combined with pterygium surgery, 265
  viscoelastic substances in, 192, 384, 512
Ophthalmology:
  departments, initial referral of children to, survey, 650
  medical, computerised diagnostic index for, 212

Ophthalmopathy, Graves':
  extraocular muscle surgery in, 481
  upper lid retraction, aetiology, in, 484
Optic:
  disc, drusen, bilaterality, metabolic malfunction and, 180
  foramen, views, in X-rays, diagnostic value, 235
  nerve: avulsion, snooker cue and, 499
    glioma, uveal melanoma and, in von Recklinghausen's neurofibromatosis, 502
    hypoplasia:
      astigmatism and, 297
      carbamezipe and epilepsy and, 511
      children, review, 300
      in CHARGE association, 421
    invasion, ciliary body melanoma and, 123
  neuropathy:
    anterior ischaemic, intraocular pressure and, 99
    hereditary, Leber's, advances, 495
    of sarcoidosis, 495
Orbit/Orbital:
  aneurysmal bone cyst of sphenoid and, 505
  contralateral, retinoblastoma metastatic to, 311
  cyst, colobomatous, microphthalmos and, 59
  decompression, bilateral failure of adduction following, 239
  emphysema, transconjunctival, traumatic, 380
  haemorrhage, induced by labour, 242
  liposarcoma, CAT findings in, 437
  radiotherapy, postenucleation, choroidal melanoma with extrascleral extension and, 36
  retinoblastoma, recurrence in, successful treatment, 97
  volume-deficient, silastic implantation and, 545
Orthoptists, 1940, 640

Paget's disease of bone:
  angioid streaks, incidence, in, 577, 579
  complications, incidence, 579
Panuveitis, lack of HLA-DR2 specificity in, 536
Patching, when safe to stop, 709
Pathology, ophthalmic, recent developments in, 786
Photocoagulation, retinal scatter, microvascular endothelial cell proliferation, prevention by vitreous, and (pig), 328
Photocoagulator, indirect ophthalmoscopic, argon, new, 233
Photographs, reliability for grading trachoma in field studies, 12
Pigments, visual, genes, new light on, 238
Pilocarpine, malignant glaucoma after laser iridectomy and, 576
Pituitary:
  adenoma, contrast sensitivity and, 358
  tumour, ptosis as early manifestation of, 188
Pneumoretinopexy, 117
Posture, intra-ocular pressure changes and, in Hansen's disease (monkey), 647
Pre-eclampsia, aldosteronism and, choriocapillaris, lobular pattern in, 702
Preventive ophthalmology, master degree programme, John Hopkins Medical Institutions, 64
Proptosis, *see* Exophthalmos
Pseudoexfoliation, precursor, precapsular film on aging lens and, 717
Pseudophakia, posterior chamber, objective autorefraction in, 731
Psychosis, self-enucleation and, 571
Pterygium, surgery, simultaneous intraocular surgery and, 265
Ptosis:
  linear scleroderma and motility disorder and, 694
  myopia and, children, 47
  pituitary tumour, early manifestation and, 188
Pupil/Pupillary:
  defect, in anterior ischaemic optic neuropathy, 99
  responses:
    in amblyopia, 676
    asymmetry, measurement, 676
  size, Lens Opacity Meter 701 measurements and, 526

Radioimmunoscintigraphy:
  with antibody 225-285, in ocular melanoma, 254
  with monoclonal antibodies to melanoma associated antigens and, choroidal melanoma and, 538
Radiotherapy:
  conjunctival malignant melanoma, 615
  melanoma, intraocular, and, 559
  orbital, postenucleation, in choroidal melanoma with extrascleral spread, 36
Refraction:
  auto-, objective, in posterior chamber pseudophakia, 731
  stabilisation, after extracapsular cataract extraction, wound closure technique and, 486
Refsum's disease, iris biopsy, electron microscopy in, 370
Retina/Retinal:
  artery:
    central, occlusion, longstanding thromboembolic disease and, homocystinuria presenting as, 696
    macroaneurysms, risk factors and natural history, 595
  detachment:
    complicated, surgery, fluorosilicone oil and, 643
    macular hole, treatment, 201
    rhegmatogenous, immunoglobulin in vitreous and subretinal fluids from patients with, 160
    surgery: fluorosilicone oil, 641, 643
      pneumoretinopexy, 117
      silicone and, 641
  dysfunction, initial ophthalmic sign in AIDS, 49
  function, diabetes and, 385, 704
  haemorrhage, in retinal macroaneurysm, 595
  laser lenses, magnification, spot size and field of view, 177
  light sensitivity in diabetic retinopathy, localised blood-retinal barrier and, 388
  necrosis:
    acute, chickenpox in adults and, 443
    syndrome, acute, mild, chickenpox chorioretinitis and, 698
  neural, ERG, in chorioretinal gyrate atrophy, 363
  photocoagulation, scatter, microvascular endothelial cell proliferation, prevention by vitreous, and (pig), 328
  pigment epithelium: ERG in chorioretinal gyrate atrophy, 363
    inflammation, ocular schistosomiasis and, 440
    tears, computerised visual field deficits in, 556
  proliferative processes, study, advances, 186
  vein:
    central: occlusion, under 40 years of age and, 30
      thrombosis, malignant glaucoma after laser iridectomy and, 576
    occlusion:
      isovolaemic haemodilution for, haemorheological changes after, 665
      risk factor for retinal macroaneurysms, 595
Retinitis, cytomegalovirus, in AIDS, intravitreal ganciclovir treatment for, 511
Retinoblastoma:
  aqueous and serum neurone-specific enolase assessment in, 427
  genetic abnormality in, 186
  immunohistological characterisation, 144
  metastatic to contralateral orbit, 311
  orbital recurrence, successful treatment, 97
Retinopathy:
  diabetic:
    early, nyctometry, value in, 106
    hypoxic viscosity and, 387, 400
    minimal, ERG in, 681
    new clue, 387
    perimetric studies in, 704
    retinal light sensitivity in, local blood-retinal barrier leakage and, 388
  in incontinentia pigmenti, diagnosis and treatment, 377
  sickle, proliferative, risk factors for, 172
  thioridazine, progression? 739
Retinopexy, pneumo-, 117
Rhinosporidiosis, conjunctival, scleral melting in, 635
Royal London Ophthalmic Hospital Reports, 1

Sarcoidosis, diagnosis, conjunctival biopsy and, 469
Saudi Arabia, cataract extraction, results and complications in, 141
Schistosomiasis, ocular, retinal pigment epithelium, inflammation, and, 440
Schizophrenic, self-enucleation and, 571
Sclera/Scleral:
  melting, conjunctival rhinosporidiosis and, 635
Scleritis, posterior, presenting as intraocular tumour, 121
Scleroderma, linear, en coup de sabre, ptosis and motility disorders and, 694
Sclerosis, multiple, MRI in, 494
Scopulariopsis brevicaulis, fungal keratitis due to, 561
Scotoma, diabetes and, 704
Silastic, implantation, volume-deficient orbit and, 545
Silicone, retinal detachment surgery and, 641
Sinus, maxillary, atrophy, enophthalmos due to, 496
Sneeze, photic, reflex, in nephrotic cystinosis, 705, 706
Snooker cue, optic nerve avulsion and, 499
Sphenoid bone, aneurysmal bone cyst, orbit and, 505
Sport, choroidal rupture, indirect, and, 208
Staphyloma, in morning glory syndrome, 56
Statpac, glaucomatous field defects, diagnosis and, size 1 stimulus and, 289
Steroids, topical, in corneal ulcer treatment, 528
Strabismus:
  children, initial referral to ophthalmology department, and, survey, 650
  convergent:
    secondary, surgery for, binocularity after, 155
    treatment, abnormal meridional hypermetropia and, 82
  family history, strabismic amblyopia diagnosis and, 589
  incidence: factors determining, longitudinal study, 589
    in high-risk and low-risk infants, 465
  treatment, operative, inadvertent globe perforation, incidence, in, 490

Streptokinase, hyphaema following, after cataract extraction, 447
Stroke syndrome, anterior ischaemic optic neuropathy and, 99
Sulphorhodamine B, conjunctival staining and, 519
Sympathetic ophthalmia, intractable, chlorambucil in, 353

The Ophthalmoscope, 1
Therapy, cytotoxic, corneal epithelial erosion following, 638
Thioridazine, retinopathy, progression? 739
TINU syndrome, in elderly woman, 53
Timolol:
  corneal sensitivity and, 409
  topical, serum lipoproteins and, 663
Tissues, ocular, relative pressure, artificial maintenance during surgery, 462
Tobacco amblyopia, yellow forelock in, 509
Tomography, computer-assisted:
  choroidal osteoma, 701
  ciliary body melanoma, 123
  extraocular muscle, *Cysticercus cellulosae* infestation, 751
  frontal bone epidermoid, 445
  maxillary atrophy causing enophthalmos and, 496
  optic nerve glioma and uveal melanoma in von Recklinghausen's neurofibromatosis, 502
  orbital haemorrhage induced by labour, 242
  orbital liposarcoma, 437
  retinoblastoma metastatic to contralateral orbit, 312
  retinoblastoma, orbital recurrence, and, 97
  traumatic transconjunctival orbital emphysema, 380
Trabecular meshwork:
  amino acid content, quantitative analysis, 280
  collagen content, quantitative analysis, glaucoma and, 280
Trabeculoplasty, diode laser, for primary open-angle glaucoma and ocular hypertension, 743
Trachoma:
  blindness due to, Kenya, 333
  grading in field studies, photographs, reliability, and, 12
  prevalence, Turkana tribe, Kenya, 85
  upper lid trichiasis surgery, standardised, in, 109
Trial frame, for children, 639
Trichiasis, upper lid, surgery, standardized, in trachoma, 109
Tuberculosis:
  conjunctival, neighbouring lupus vulgaris lesion and, 315
  miliary, disseminated choroidal haemorrhages and, 317
Turkana tribe, Kenya, ophthalmic disease, prevalence in, 84

Ultrasonography:
  posterior scleritis presenting as intraocular tumour and, 121
  uveal melanoma thickness measurement, interobserver variability and, 183
United Kingdom, corneal tissue supply in, 685
Uvea/Uveal:
  melanoma: malignant, optic nerve glioma and, in von Recklinghausen's neurofibromatosis, 502
    thickness, ultrasonography and, interobserver variability, 183
Uveitis:
  cyclosporin A, ocular distribution, in, 350
  glaucoma in, retrospective study, 223
  idiopathic, chronic, severe, cyclosporin in, 344
  ocular brucellosis and, 249
  posterior:
    endogenous, review, 620
    multifocal, clinical and pathological findings in, 688
  tubulointerstitial nephritis and, syndrome, in elderly woman, 53
Uveoretinitis, posterior, experimental models, 621

Vagotomy, functional, unilateral forced right nostril breathing and, intraocular pressure and, 607
Virus/Viruses:
  cytomegalo-, retinitis, in AIDS, intravitreal ganciclovir for, 511
  entero-, acute haemorrhagic conjunctivitis and, Nigeria, 89
  herpes simplex:
    disease induced by, corneal oedema and (rabbit), 723
    ocular and oral shedding, 114
    ocular infection: antiviral drug sensitivity in, 532
      reduced sensitivity to acyclovir in primary disease, 286
  human immunodeficiency infection, gonococcal keratoconjunctivitis and, 52
Viscoelastic substances, in ophthalmic surgery, 192, 384, 512
Vision:
  binocular, surgery for secondary esotropia in childhood and, 155
  defects, in geographically defined population of 2-year-olds, 465
  poor, initial detection, children, 650
Visual:
  acuity, *see* Acuity, visual
  evoked potentials, flash, albinism in children and, 136
  Fields, *see* Fields, visual
  function, thioridazine retinopathy and, 739
  pigments, *see* Pigments, visual
Vitroretinopathy, proliferative membranes, components, changes, immunohistochemical studies, 393
Vitreous:
  haemorrhage: in HELLP syndrome, 498
    in retinal macroaneurysm, 595
  immunoglobulins, rhegmatogenous retinal detachment and, 160
  proliferative processes, study, advances, 186

Weill-Marchesani syndrome, lens histology in, 631
Wilmer Institute, endowed lectureship, 192
Wilms' tumour, 11p 13 deletion and aniridia and, 568

Xanthomatosis, cerebrotendinous, II, cataractous lens, sterol content, in, 629
Xeroderma pigmentosum, malignant fibrous conjunctival histiocytoma and, 624
Xerophthalmia, prevalence, Turkana tribe, Kenya, 85
X-ray, 'optic foramen views', diagnostic value, 235

Yellow forelock, tobacco amblyopia and, 509

Zinc, aqueous and serum concentrations, in glaucoma and cataract, 661

BRITISH JOURNAL OF OPHTHALMOLOGY

VOLUME 74 · 1990

Editor: Redmond J H Smith
Assistant Editors: W S Foulds
M D Sanders

EDITORIAL COMMITTEE

Desmond Archer
A C Bird
A H Chignell
David Easty
Peter Fells
J V Forrester
A Garner
Ian Grierson
John Hungerford
Noel Rice
D J Spalton
John Wright
Editor
British Medical Journal

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

VOLUME 74 · CONTENTS

No 1 JANUARY 1990

Page

Editorials

1 The *BJO* in the 1990s *Redmond Smith*
1 Glaucoma: is there light at the end of the tunnel? *Redmond Smith*

Original articles

3 Association between intraocular pressure and loss of visual field in chronic simple glaucoma *R Vogel, R P Crick, R B Newson, M Shipley, H Blackmore, C J Bulpitt*
7 Effect of donor parameters on primary graft failure and the recovery of acuity after keratoplasty *Brett L Halliday, Sybil A Ritten*
12 Reliability of photographs for grading trachoma in field studies *Sheila K West, Hugh R Taylor*
14 Histopathological findings in the iris of dapsone treated leprosy patients *F Brandt, H M Zhou, Z R Shi, N Rai, L Thuladar, H Pradhan*
19 Topical use of indomethacin on the day of cataract surgery *A E T Searle, J L Pearce, D E Shaw*
22 Pseudophakic accommodation? A study of the stability of capsular bag supported, one piece, rigid tripod, or soft flexible implants *S J Hardman Lea, M P Rubinstein, M P Snead, S M Haworth*
26 *Bacillus*-induced endophthalmitis: new series of 10 cases and review of the literature *Ramzi Hemady, Mandi Zaltas, Barbara Paton, C Stephen Foster, Ann S Baker*
30 Central retinal vein occlusion in people aged 40 years or less: a review of 17 patients *R F Walters, D J Spalton*
36 Postenucleation orbital radiotherapy for the treatment of malignant melanoma of the choroid with extrascleral extension *P G Hykin, A C E McCartney, P N Plowman, J L Hungerford*
40 Topical fluconazole for experimental candida keratitis in rabbits *Wolfgang Behrens-Baumann, Bernd Klinge, Reinhard Ruchel*
43 Magnetic resonance imaging of juxtapapillary plaques in cadaver eyes *David F Williams, William F Mieler, Glenn J Jaffe, Dennis M Robertson, Lloyd Hendrix*

Mini review

47 Aetiology of myopia *Calbert I Phillips*

Case reports

49 Retinal dysfunction as an initial ophthalmic sign in AIDS *Scott E Brodie, Alan H Friedman*
52 Adult gonococcal keratoconjunctivitis with AIDS *R K W Lau, B T Goh, S Estreich, S N Cox, I Levy*
53 Acute tubulointerstitial nephritis and uveitis syndrome in the elderly *P Salu, N Stempels, K Vanden Houte, D Verbeelen*
56 Morning glory syndrome: a histopathological study *Willem A Manschot*
59 Microphthalmos with colobomatous orbital cyst. clinical, histological, immunohistological, and electron microscopic findings *W Lieb, R Rochels, U Gronemeyer*
63 **Letters to the editor · Book reviews · Notes**

No 2 FEBRUARY 1990

Editorials

65 The living contact lens *Redmond Smith*
66 Paediatric cataract surgery *Redmond Smith*

Original articles

67 Epikeratophakia for aphakia, keratoconus, and myopia *Brett L Halliday*
73 Lens surgery in infancy and childhood *Stephen Hing, Lynne Speedwell, David Taylor*
78 Quantification of lens opacification with a commercially available lensometer *S J Tuft, F W Fitzke, J Lawrenson, J Silver, J Marshall*
82 Factors relating to visual acuity in children who have been treated for convergent squint *R M Ingram, C Walker, B Billingham, J Lucas, S Dally*
84 A prevalence survey of ophthalmic diseases among the Turkana tribe in north-west Kenya *Ron Loewenthal, Jacob Pe'er*
89 An outbreak of acute haemorrhagic conjunctivitis in Kaduna, Nigeria *O E Babalola, S S Amoni, E Samaila, U Thaker, S Darougar*
93 Chorioretinal neovascular membranes complicating contusional eye injuries with indirect choroidal ruptures *C M Wood, J Richardson*
97 Orbital recurrence of retinoblastoma successfully treated by combined therapy *R R Goble, J McKenzie, J E Kingston, P N Plowman, J L Hungerford*
99 Anterior ischaemic optic neuropathy and intraocular pressure *B Katz, R N Weinreb, D T Wheeler, M R Klauber*
103 Cyclocryotherapy: a review of cases over a 10-year period *M T Benson, M E Nelson*
106 Macular recovery function (nyctometry) in diabetics without and with early retinopathy *E Midena, T Segato, M Giuliano, M Zucchetto*
109 A trial of surgery for trichiasis of the upper lid from trachoma *M H Reacher, M J E Huber, R Canagaratnam, A Alghassany*
114 Ocular shedding of herpes simplex virus *S B Kaye, N Madan, T C Dowd, C A Hart, K McCarthy, A Patterson*

Mini review

117 Pneumoretinopexy: a personal view *A H Chignell*

Case reports

118 Infective conjunctivitis and corneal scarring in three brothers with sex linked hypogammaglobulinaemia (Bruton's disease) *T T Hansel, D P O'Neill, M L Yee, J M Gibson, R A Thompson*
121 Posterior scleritis as an intraocular tumour *Paul T Finger, Henry D Perry, Samuel Packer, Richard A Erdey, Geoffrey D Weisman, Patrick A Sibony*
123 Ciliary body melanoma with optic nerve invasion *Saad Al-Haddab, Ahmed Hidayat, Khalid F Tabbara*
125 **Letters to the editor · Notes · Book reviews**

No 3 MARCH 1990

Editorials

129 Contamination of contact lens storage cases *John Dart*
130 Albinism and anatomy *Redmond Smith*
130 Cataract surgery *Arthur Steele*

131 Histogenesis of retinoblastoma *John Hungerford*

Original articles

133 Contamination of contact lens storage cases by *Acanthamoeba* and bacteria *D F P Larkin, S Kilvington, D L Easty*
136 Albinism in childhood: a flash VEP and ERG study *Isabelle Russell-Eggitt, A Kriss, D S I Taylor*
141 Visual outcome and complications after cataract extraction in Saudi Arabia *Mubarak F Al Faran*
144 Immunohistological characterisation of retinoblastoma and related ocular tissue *John F Tarlton, David L Easty*
150 Contact lenses for infant aphakia *Luis G Amaya, Lynne Speedwell, David Taylor*
155 Binocularity following surgery for secondary esotropia in childhood *Catherine N Smoot, John W Simon, Leonard B Nelson*
158 Results of a randomised trial of treating abnormal hypermetropia from the age of 6 months *R M Ingram, P E Arnold, S Dally, J Lucas*
160 Immunoglobulins in paired specimens of vitreous and subretinal fluids from patients with rhegmatogenous retinal detachment *Geoffrey E Rose, Brenda M Billington, A H Chignell*
163 External ocular findings in lupus erythematosus: a clinical and immunopathological study *Peggy Frith, S M Burge, P R Millard, F Wojnarowska*
168 Corneal oxygenation: blink frequency as a variable in rigid contact lens wear *Barbara A Fink, Richard M Hill, Leo G Carney*
172 Risk factors for proliferative sickle retinopathy *Peter D Fox, David T Dunn, Joanne S Morris, Graham R Serjeant*
177 Retinal laser lenses: magnification, spot prize, and field of view *Martin A Mainster, Janet L Crossman, Phillip J Erickson, Gregory L Heacock*
180 Bilaterality of drusen *M Barondes, D Pauleikhoff, I C Chisholm, D Minassian, A C Bird*
183 Ultrasonographic measurement of uveal melanoma thickness: interobserver variability *Devron H Char, Stewart Kroll, Robert D Stone, Roger Harrie, Barry Kerman*

Mini review

186 Some recent developments in ophthalmic pathology *Alec Garner*

Case report

188 Ptosis as the early manifestation of pituitary tumour *May Yung Yen, Jorn Hon Liu, Sheng Ji Jaw*

192 **Book reviews · Letter to the editor · Notes**

No 4 APRIL 1990

Editorials

193 Are there two varieties of primary open-angle glaucoma? *Redmond Smith*
194 Getting an air lock on the macular hole *Redmond Smith*
195 Local anaesthesia for cataract surgery *Arthur Steele*

Original articles

196 Biostatistical evidence for two distinct chronic open angle glaucoma populations *Michael Schulzer, Stephen M Drance, Cecric J Carter, Donald E Brooks, Gordon R Douglas, Wing Lau*
201 Treatment of macular hole retinal detachment *Yoon-Kee Lai*
203 Extracapsular cataract extraction under local anaesthesia without retrobulbar injection *R M Redmond, N L Dallas*
205 Cataract extraction without retrobulbar anaesthetic injection *Redmond Smith*
208 Indirect choroidal ruptures: aetiological factors, patterns of ocular damage, and final visual outcome *Christopher Mark Wood, John Richardson*
212 A computerised diagnostic index for medical and neuro-ophthalmology *W H Woon, D J Spalton*
215 Brightness discrimination and contrast sensitivity in chronic glaucoma – a clinical study *Su Lin Teoh, Donald Allan, Gordon N Dutton, Wallace S Foulds*
220 Calculating the predictive power of the Henson field screener in a population at risk of glaucomatous field loss *Stephen A Vernon, Donald J Henry, Susan J Jones*
223 Glaucoma in patients with uveitis *William C Panek, Gary N Holland, David E Lee, Robert E Christensen*
228 Ultrastructural distribution of collagen types I-VI in aging human retinal vessels *G E Marshall, A G Konstas, W R Lee*
233 Argon indirect ophthalmoscopic photocoagulation: reduced potential phototoxicity with a fixed safety filter *Marc M Whitacre, Nubar Manoukian, Martin A Mainster*
235 Diagnostic value of 'optic foremen views': experience from an eye hospital *Ivan Moseley*

Mini review

238 New light on visual pigment genes *Barrie Jay*

Case reports

239 Bilateral failure of adduction following orbital decompression *F Kinsella, P Kyle, A Stansfield*
242 Orbital haemorrhage induced by labour *Orna Geyer, Daniel Wasserman, Leonard Rothkoff, Moshe Lazar*
243 Loss of vision in one eye following scoliosis surgery *J West, G Askin, M Clarke, S A Vernon*
245 Ocular cowpox: transmission from the domestic cat to man *Gerard M O'Connor, Arun Acalam A Thiru, Owen E Caul*
247 Mixed haematogenous endophthalmitis caused by *Candida albicans* and CDC fermentative corynebacterium group A-4 *Caroline Barker, Jane Leitch, N P Brenwald, M Farrington*
249 Ocular brucellosis *Khalid F Tabbara, Hassan Al-Kassimi*
251 External ocular pigmentation secondary to perforating eye injury *Mark T Benson, Ian Rennie, John Talbot*

254 **Letters to the editor · Book reviews · Notes**

No 5 MAY 1990

Editorial

257 How safe are intraocular lenses? *Redmond Smith*

Original articles

258 Corneal endothelial changes after posterior chamber intraocular lens implantation in patients with or without diabetes mellitus *Nanako Furuse, Seiji Hayasaka, Yukari Yamamoto, Tomoichi Setogawa*
261 Manipulative damage to the endothelium of infant and adult donor corneas *Israel N Nartey, Emil S Sherrard, Arthur D McG Steele*
265 Simultaneous pterygium and intraocular surgery *Brendan I Ibechukwu*
267 The lens after renal transplantation *G Adrien Shun-Shin, Peter Ratcliffe, Anthony J Bron, Nicholas P Brown, John M Sparrow*
272 Persistently raised intraocular pressure following extracapsular cataract extraction *R David, Z Tessler, R Yagev, D Briscoe, B Z Biedner, E Gilad, Y Yassur*
275 Computer assisted analysis of fluorescein videoangiograms *Paul A R Meyer, Fred W Fitzke*

278 Convergence excess esotropia treated surgically with fadenoperation and medial rectus muscle recessions *R Jane Leitch, John P Burke, Ian M Strachan*
280 Quantitative analysis of collagen content and amino acids in trabecular meshwork *Ian Finkelstein, Graham E Trope, Prasanta K Basu, Syed M Hasany, William S Hunter*
283 A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis *S M Porter, A Patterson, P Kho*
286 Ocular herpes simplex virus infections: reduced sensitivity to acyclovir in primary disease *S J Charles, J J Gray*
289 Detecting early glaucomatous field defects with the size I stimulus and Statpac *Alan H Zalta, John C Burchfield*
294 Biomicroscopic examination of the ocular fundus with a +150 dioptre lens *Nicholas Blaire Lee*
297 Optic nerve hypoplasia and astigmatism: a new association *Sabah M Zeki*

Mini review

300 Optic nerve hypoplasia in children *Sabah M Zeiki, Gordon N Dutton*

Case reports

305 Colour Doppler imaging in the demonstration of an orbital varix *Wolfgang E Lieb, Daniel A Merton, Jerry A Shields, Steven M Cohen, Donald D Mitchell, Barry B Goldberg*
309 Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm *P Corridan, S Nightingale, N Mashoudi, A C Williams*
311 Retinoblastoma metastatic to the contralateral orbit *Kanwar Mohan, Amod Gupta, J S Saini, Subhadra Jalali, Kusum Joshi*
313 Accelerated ocular neovascularisation in diabetics following posterior chamber lens implantation *P Prasad, P H Setna, J A Dunne*
315 Tuberculosis of the conjunctiva occurring in association with a neighbouring lupus vulgaris lesion *C D Cook, M Hainsworth*
317 A case of miliary tuberculosis with disseminated choroidal haemorrhages *Takashi Shiono, Shin-ichi Abe, Toshio Horiuchi*

320 **Letters to the editor · Book reviews · Correction**

No 6 JUNE 1990

Editorials

321 Lyme disease *D J Spalton*
323 Neovascularisation again *Redmond Smith*
324 Not enough cataract surgeons *Redmond Smith*

Original articles

325 Ocular Lyme disease: case report and review of the literature *Danny J H Kauffmann, Gary P Wormser*
328 Inhibition of microvascular endothelial cell proliferation by vitreous following retinal scatter photocoagulation *Arvind Singh, Mike Boulton, Carol Lane, John Forrester, Joe Gaal, David McLeod*
333 Blindness and eye disease in Kenya: ocular status survey results from the Kenya Rural Blindness Prevention Project *Randolph Whitfield, Larry Schwab, Dennis Ross-Degnan, Paul Steinkuller, Jack Swartwood*
341 3·8 Million blinded by cataract each year: projections from the first epidemiological study of incidence of cataract blindness in India *D C Minassian, V Mehra*
344 Cyclosporin in the treatment of severe chronic idiopathic uveitis *J de Vries, G S Baarsma, M J W Zaal, T N Boen-Tan, A Rothova, H J Buitenhuis, C M C Schweitzer, R J W de Keizer, A Kylstra*
350 Ocular penetration of cyclosporin A. III: The human eye *David BenEzra, Genia Maftzir, Christian de Courten, Pentti Timonen*
353 High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's disease *Howard H Tessler, Tom Jennings*
358 Contrast sensitivity function and pituitary adenoma: a study of 40 cases *M Grochowicki, A Vighetto, S Berquet, G Sassolas*
359 Changes in height of choroidal melanomas after plaque therapy *David H Abramson, Camille A Servodidio, Beryl McCormick, Daniel Fass, Edith Zang*
363 Gyrate atrophy of the choroid and retina: ERG of the neural retina and the pigment epithelium *Christina Raitta, Synnove Carlson, Kaarina Vannas-Sulonen*

Mini review

368 Anterior segment surgery *M J Roper-Hall*

Case reports

370 Refsum's disease: electron microscopy of an iris biopsy *Andrew D Dick, Jonathan Jagger, Alison C E McCartney*
373 Mucinous adenocarcinoma metastatic to the iris, ciliary body, and choroid *Wolfgang E Lieb, Jerry A Shields, Carol L Shields, George L Spaeth*
377 Early diagnosis of the retinopathy of incontinentia pigmenti: successful treatment by cryotherapy *J Rahi, J Hungerford*
380 Traumatic transconjunctival orbital emphysema *Edward M Stroh, Paul T Finger*
382 Glaucoma in siblings with Morquio syndrome *M Cahane, G Triester, F A Abraham, S Melamed*

384 **Letters to the editor · Note**

No 7 JULY 1990

Editorials

385 Diabetes and retinal function *Redmond Smith*
386 Natural history of epiretinal membranes *Redmond Smith*
387 Diabetic retinopathy; a new clue in the puzzle *Redmond Smith*

Original articles

388 Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy *Toke Bek, Henrik Lund-Andersen*
393 Variation in epiretinal membrane components with clinical duration of the proliferative tissue *I Morino, P Hiscott, N McKechnie, I Grierson*
400 Hypoxic viscosity and diabetic retinopathy *T Rimmer, J Fleming, E M Kohner*
405 A single dose of the topical carbonic anhydrase inhibitor MK-927 decreases IOP in patients *N Pfeiffer, R Hennekes, E A Lippa, F Grehn, H Garus, F L Brunner-Ferber*
409 Effects of topical timolol (0·5%) and betaxolol (0·5%) on corneal sensitivity *S S Weissman, P A Asbell*
413 Comparison of the effect of acetazolamide tablets and Sustets on diurnal intraocular pressure in patients with chronic simple glaucoma *P W Joyce, K B Mills*

417 Outcome of iatrogenic choroidal neovascularisation in sickle cell disease *Peter D Fox, Robert W Acheson, Graham R Serjeant*

421 The eye in the CHARGE association *I M Russell-Eggitt, K D Blake, D S I Taylor, R K H Wyse*

427 Electrophoretic assessment of aqueous and serum neurone-specific enolase in retinoblastoma and ocular malignant melanoma *B S F Shine, J Hungerford, B Vaghela, G A K Sheraidah*

Mini review

431 Ocular fluorophotophotometry *D J Spalton*

Case reports

433 Endogenous *Nocardia asteroides* endophthalmitis in a patient with systemic lupus erythematosus *Y Ishibashi, R Watanabe, S Hommura, A Koyama, T Ishikawa, Y Mikami*

437 Primary orbital liposarcoma: clinical and computed tomographic features *Alan A McNab, Ivan Moseley*

440 Inflammation of the retinal pigment epithelium: a unique presentation of ocular schistosomiasis *A Jane Dickinson, A Ralph Rosenthal, Karl G Nicholson*

443 Acute retinal necrosis as a novel complication of chickenpox in adults *T Matsuo, M Koyama, N Matsuo*

445 Frontal bone epidermoid – a rare cause of proptosis *C R Chowdhury, C M Wood, P R Samuel, J Richardson*

447 **Letters to the editor · Book reviews · Notes**

No 8 AUGUST 1990

Editorial

449 Exfoliation syndrome *A Garner*

Original articles

450 Immunogold localisation of laminin in normal and exfoliative iris *A G Konstas, G E Marshall, W R Lee*

458 Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules *A P Watson, E S Rosen*

462 Artificial maintenance of the relative ocular tissue pressure during eye surgery *C Maggi, R Maggi*

465 Ocular and visual defects in a geographically defined population of 2-year-old children *Maureen Stayte, Ann Johnson, Catherine Wortham*

469 Conjunctival biopsy in the diagnosis of sarcoidosis *Richard F Spaide, David L Ward*

472 Changes in waveform of congenital nystagmus associated with biofeedback treatment *Mikako Mesawa, Satoshi Ishikawa, Kazuhiko Ukai*

477 A study of the causes of non-compliance by patients prescribed eyedrops *A J Winfield, D Jessiman, A Williams, L Esakowitz*

481 Extraocular muscle surgery for Graves' ophthalmopathy: does prior treatment influence surgical outcome? *Maarten Ph Mourits, Leo Koorneef, Ada M van Mourik-Noordenbos, Helma M van der Meulen-Schot, Mark F Prummel, Wilmar M Wiersinga, Arie Berghout*

484 Graves' ophthalmopathy: V. Aetiology of upper eyelid retraction in Graves' ophthalmopathy *Steven E Feldon, Lori Levin*

486 Stabilisation of refraction following extracapsular cataract extraction *P Baranyovits*

490 Incidence of inadvertent globe perforation during strabismus surgery *R J Morris, P H Rosen, P Fells*

Mini review

494 Neuro-ophthalmology *M D Sanders*

Case reports

496 Hemifacial atrophy: an unusual cause of enophthalmos *K N Hakin, C Yokoyama, J E Wright*

498 Vitreous haemorrhage as a complication of HELLP syndrome *Steven R Leff, David L Yarian, Leo Masciulli, Stuart N Green, Roy E Baldomero*

499 Optic nerve avulsion due to forced rotation of the globe by a snooker cue *P G Hykin, I D Gardner, S M Wheatcroft*

502 Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis *C Mark Antle, Karim F Damji, Valerie A White, Jack Rootman*

505 Aneurysmal bone cyst of the sphenoid with orbital involvement *Jill V Hunter, Cheryl Yokoyama, Ivan F Moseley, John E Wright*

509 Yellow forelock – a new neuro-ophthalmological sign *R I Kellen, B Schrank, R M Burde*

511 **Book review · Letters to the editor**

No. 9 SEPTEMBER 1990

Editorial

513 Lye in the eye *Redmond Smith*

Original articles

514 Eye injuries from assault with chemicals *John D L Beare*

519 Staining of the conjunctiva and conjunctival tear film *Joseph A Eliason, David M Maurice*

523 Acute closed-angle glaucoma and Nd-YAG laser iridotomy *D C Saunders*

526 Influence of pupil size on measurements made with the Lens Opacity Meter 701 *Michael P Clarke, James C G Pearson, Stephen A Vernon, J Colin Matthews*

528 Topical steroids in the treatment of central and paracentral corneal ulcers *T R Carmichael, Y Gelfand, N H Welsh*

532 Antiviral drug sensitivity in ocular herpes simplex virus infection *M J Menage, E de Clercq, A van Lierde, V S Easty, J M Darville, S D Cook, D L Easty*

536 Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis *Richard F Spaide, John E Skerry, Lawrence A Yannuzzi, Janet T DeRosa*

538 Radioimmunoscintigraphy and immunohistochemistry with melanoma-associated monoclonal antibodies in choroidal melanoma: a comparison of the clinical and immunohistochemical results *D F Schaling, J P van der Pol, M J Jager, M J P G van Kroonenburgh, J A Oosterhuis, D J Ruiter*

542 Congenital eyelid retraction *J R O Collin, L Allen, S Castronuovo*

545 The volume-deficient orbit: clinical characteristics, surgical management, and results after extraperiorbital implantation of Silastic block *Geoffrey E Rose, Harold Sigurdsson, Richard Collin*

551 Experimental *Acanthamoeba* keratitis: I. Preliminary findings *D F P Larkin, D L Easty*

556 Computerised visual field deficits in tears of the retinal pigment epithelium *Joseph I Maguire, William H Annesley Jr, William L Decker, Gary C Brown, David H Fischer, Joan M Slagle*

Mini review

559 Management of intraocular melanoma *Wallace S Foulds*

Case reports

561 A case of fungal keratitis caused by *Scopulariopsis brevicaulis:* treatment with antifungal agents and penetrating keratoplasty *Nicola K Ragge, J C Dean Hart, D L Easty, A G Tyers*
563 Traumatic hyphaema in a haemophiliac *C D G Morsman, J Holmes*
564 Spontaneous reabsorption of a rubella cataract *George T H Smith, G Adrien Shun-Shin, Anthony J Bron*
566 Progression of an iris melanoma over 41 years *David G Charteris*
568 11p13 Deletion, Wilms' tumour, and aniridia: unusual genetic, non-ocular and ocular features of three cases *Véronique Jotterand, Hélène M Boisjoly, Carmen Harnois, Pierre Bigonesse, Rachel Laframboise, Richard Gagné, André St-Pierre*
571 Self-enucleation and psychosis *Nicholas P Jones*
574 Lymphangioma circumscriptum of the eyelids and conjunctiva *R R Goble, M A Frangoulis*
576 **Letters to the editor · Note · Fifty years ago**

No 10 OCTOBER 1990

Editorial

577 Paget's disease and angioid streaks: one complication less? *Redmond Smith*

Original articles

579 Prevalence of angioid streaks and other ocular complications of Paget's disease of bone *T R Dabbs, K Skjodt*
583 How large must an iridotomy be? *B W Fleck*
589 A longitudinal study of children with a family history of strabismus: factors determining the incidence of strabismus *E Aurell, K Norrsell*
595 Retinal arterial macroaneurysms: risk factors and natural history *Robert W Panton, Morton F Goldberg, Marilyn D Farber*
601 The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma *John F Pitts, Jeffrey L Jay*
605 Effect of a β-blocker on altered body position: induced ocular hypertension *Dean A Smith, Graham E Trope*
607 A functional vagotomy induced by unilateral forced right nostril breathing decreases intraocular pressure in open and closed angle glaucoma *Joshua Backon, Nelson Matamoros, Manuel Ramirez, Rodrigo M Sanchez, Jaime Ferrer, Alberto Brown, Uriel Ticho*
610 Choroidal lesions in patients with AIDS *Marc A Rosenblatt, Carol Cunningham, Steven Teich, Alan H Friedman*
615 Therapeutic outcome of patients suffering from malignant melanomas of the conjunctiva *P K Lommatzsch, R E Lommatzsch, I Kirsch, P Fuhrmann*

Mini review

620 Endogenous posterior uveitis *J V Forrester*

Case reports

624 Malignant fibrous histiocytoma of the conjunctiva *Jacob Pe'er, Shmuel Levinger, Michael Ilsar, Harold Climenhaga, Elimelech Okon*
629 A case of cerebrotendinous xanthomatosis. II: the sterol content of a cataractous lens *P McKenna, S J Morgan, R G Bosanquet, M F Laker*
631 Histology of the lens in the Weill-Marchesani syndrome *Hisako Fujiwara, Yasushi Takigawa, Shinya Ueno, Kanshi Okuda*
635 Scleral melting in a patient with conjunctival rhinosporidiosis *R M L De Doncker, R J W de Keizer, J A Oosterhuis, A Maes*
638 Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy *A Hirsh, A Alhalel, A Weiss, H Brener, I Avni*

639 **Letters to the editor · Notes · 50 Years Ago**

No 11 NOVEMBER 1990

Editorial

641 Fluorosilicone oil for retinal detachment *J D Scott*

Original articles

643 Fluorosilicone oil in the treatment of retinal detachment *Charles M Gremillion Jr, Gholam A Peyman, Kwan-Rong Liu, Khaled S Naguib*
647 Intraocular pressure changes and postural changes of intraocular pressure in experimentally induced Hansen's disease of rhesus, mangabey, and African green monkeys *Naushad Hussein, Bruce Ostler, Bobby J Gormus, Robert Wolf, Gerald P Walsh*
650 A survey of the initial referral of children to an ophthalmology department *Wang Yu-dong, J R Thompson, D B Goulstine, A R Rosenthal*
654 Biometry of the crystalline lens in early-onset diabetes *John M Sparrow, Anthony J Bron, Nicholas A Phelps Brown, H A W Neil*
661 Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract *Nurettin Akyol, Orhan Değer, E Edip Keha, Saim Kiliç*
663 Topical timolol and serum lipoproteins *James West, Simon Longstaff*
665 Haemorheological changes in patients with retinal vein occlusion after isovolaemic haemodilution *J Wiek, M Schade, M Wiederholt, H R Arntz, L L Hansen*
670 Cytopathology of adenovirus keratitis by replica technique *Prabhat C Maudgal*
676 Pupillary responses in amblyopia *Alison Y Firth*
681 The electroretinogram in minimal diabetic retinopathy *T C A Jenkins, J P Cartwright*

Mini review

685 Supply of corneal tissue in the United Kingdom *W J Armitage, S J Moss, D L Easty, B A Bradley*

Case reports

688 Multifocal posterior uveitis: clinical and pathological findings *David G Charteris, William R Lee*
694 Linear scleroderma associated with ptosis and motility disorders *Maria S A Suttorp-Schulten, Leo Koornneef*
696 Homocystinuria presenting as central retinal artery occlusion and longstanding thromboembolic disease *W v d Berg, F D Verbraak, P J M Bos*
698 Chickenpox chorioretinitis *S P Kelly, A R Rosenthal*
700 Choroidal osteoma (osseous choristoma): an atypical case *G Cennamo, G Iaccarino, G de Crecchio, G Liguori*
702 Lobular pattern of choriocapillaris in pre-eclampsia with aldosteronism *Yoshihiro Saito, Tatsuya Omoto, Masakatsu Fukuda*

704 **Letters to the editor · Fifty years ago**

Contents

No 12 DECEMBER 1990

Editorial

705 Photic sneezes *Redmond Smith*

Original articles

706 Photic sneeze reflex in nephropathic cystinosis *Barrett Katz, Ronald B Melles, Michael R Swenson, Jerry A Schneider*
709 When is it safe to stop patching? *John G Oster, John W Simon, Paul Jenkins*
712 Peripheral contrast sensitivity in glaucoma and ocular hypertension *Fernando Falcão-Reis, Eamonn O'Donoghue, Rosaria Buceti, Roger A Hitchings, Geoffrey B Arden*
717 Precapsular film on the aging human lens: precursor of pseudoexfoliation? *Anthony J Dark, Barbara W Streeten*
723 Pathogenesis of corneal oedema associated with herpetic eye disease *William J O'Brien, Julie Guy, Jerry L Taylor*
731 Objective autorefraction in posterior chamber pseudophakia *Palaniswamy Sunder Raj, Tayo Akingbehin, Anthony M Levy*
734 Randomised single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery *C D G Jenkins, P J McDonnell, D J Spalton*
739 Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function *Michael F Marmor*
743 Diode laser trabeculoplasty (DLT) for primary open-angle glaucoma and ocular hypertension *Dominic McHugh, John Marshall, Timothy J ffytche, Peter A M Hamilton, Anthony Raven*

Case reports

748 Atraumatic iris cilia *G I S Mackintosh, M C Grayson*
750 Infectious mononucleosis presenting as bilateral acute dacryocystitis *P L Atkinson, A M Ansons, A Patterson*
751 Infestation of extraocular muscle by *Cysticercus cellulosae* *David A DiLoreto, Ross A Kennedy, Janet M Neigel, Jack Rootman*

DIXEY

We manufacture a full range of Ophthalmic Instruments including **Micro Westcotts Scissors Gills Welsh Vannas Scissors** with 11mm Blades **Micro Castroviejos Forceps** with 0.12mm Teeth and **Kelman Macpherson Forceps**

DIXEY INSTRUMENTS LIMITED
Ophthalmic Instruments & Apparatus
19 Wigmore Street
London W1H 9LA England
Telephone: 01-580 1713 Telex: 268312

Look what's behind our innovative ophthalmic products.

At Pharmacia, our reputation for innovation is matched only by our commitment to providing an efficient service back-up.

To satisfy the increasing demand for urgent deliveries of Healonid® and IOLs, we offer:

- **24 hour delivery.**
- **Courier services.**
- **Personal delivery.**

In addition, our customers also enjoy: free resterilization of lenses; lens consignments; clinical literature search and educational courses/seminars.

For further details, contact our Customer Services Team; Birgitta Keenan and Jackie Bates direct on 0908 670413.

Pharmacia Limited
Pharmacia House, Midsummer Boulevard,
Milton Keynes MK9 3HP
Telephone: (0908) 661101
(24 hour answering service)

Pharmacia

Advancing The New Biology

NEW FORMULATION
When
nature runs dry . . .
HYPOTONIC
LIQUIFILM®
polyvinyl alcohol
TEARS
NEW HYPOTONIC FORMULATION
to help restore normal tearfilm tonicity
in lipid, aqueous and mucin deficient eyes[1]
FOR SUCCESS FROM THE START – FIRST TIME

1 MAY 1991

Liquifilm Tears Prescribing Information
Presentation: Clear, colourless to slightly straw-coloured, sterile, aqueous ophthalmic solution containing Liquifilm (polyvinyl alcohol) USP 1.4% (w/v). Also contains disodium edetate Ph Eur 0.015% (w/v), benzalkonium chloride Ph Eur 0.005% (w/v) with sodium chloride Ph Eur, sodium phosphate Ph Eur and purified water Ph Eur. **Uses:** Liquifilm Tears is an ocular lubricant for the relief of dry eye and dry eye symptoms. **Dosage and administration:** For all ages. One or two drops administered topically to the affected eye(s) as required. **Contra-indications, warnings etc:** *Contra-indications:* Sensitivity to any of the components. Not for use with soft (hydrophilic) contact lenses because of the presence of benzalkonium chloride as a preservative. *Warnings:* If irritation increases or persists, discontinue use. **Pharmaceutical precautions:** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category:** P. **Package quantities:** LIQUIFILM TEARS is available in plastic dropper bottles containing 15 ml. **Basic NHS Cost:** (as at November 1988) £1.33. **Further Information:** Nil. **Product Licence Number:** PL 0426/0009R. **Date of preparation:** July 1988. **Reference:** 1. Bron AJ. Trans Ophthalmol Soc U.K. (1985); **104:** 801-826.

ALLERGAN PHARMACEUTICALS TM
SCIENCE WITH VISION

Full prescribing information is available on request.
Allergan Limited, High Wycombe, Bucks. HP12 3SH. ®denotes registered trade mark